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THE UNIVERSITY OF ALBERTA

STUDIES ON THE TOTAL SYNTHESIS OF MEXICANOLIDE

by

TEOFILO DIECK ABULARACH

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

DOCTOR OF PHILOSOPHY

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EDMONTON, ALBERTA

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submitted by TEOFILO DIECK ABULARACH

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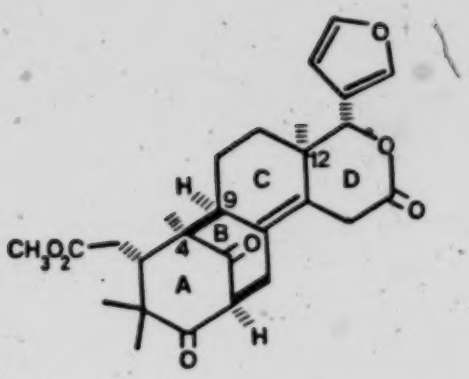
DATE July 5/1984

ABSTRACT

A highly convergent approach toward the total synthesis of the limonoid mexicanolide (I) has been explored. Central to this strategy was the expectation that a double Michael addition of diketo acid II to diene lactone III would provide mexicanolide *via* the intermediacy of seco acid IV. Compound II was readily prepared in optically active form using *d*-camphorsulfonic acid V as the starting material. Treatment of V with fused potassium hydroxide gave (+)-campholenic acid VI which was converted to the corresponding methyl ester VII using dimethyl sulfate in refluxing acetone containing potassium carbonate. Sequential treatment of VII with lithium diisopropylamide and methyl iodide furnished a single monomethylated product VIII in excellent overall yield. Ozonolysis of VIII in methylene chloride and methanol followed by reductive workup with triphenylphosphine gave a keto aldehyde which was immediately oxidized with Jones reagent to afford keto acid IX. Subsequent treatment of IX with lithium *t*-butoxide in refluxing dimethoxyethane gave diketo acid II as a single epimer.



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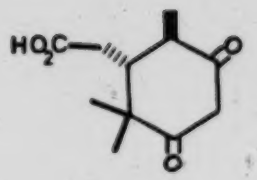

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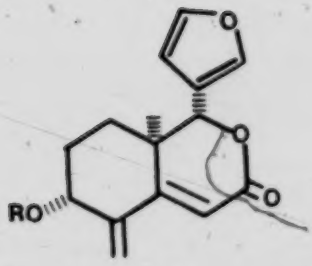

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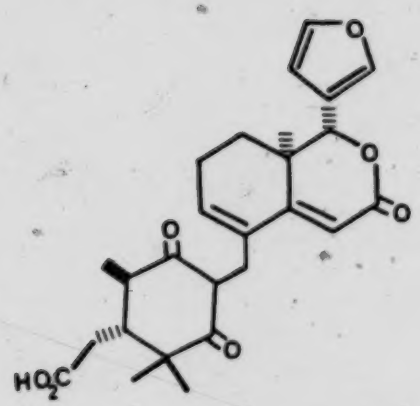

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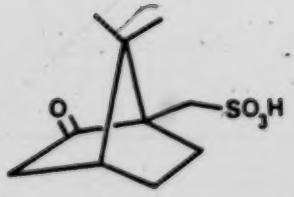

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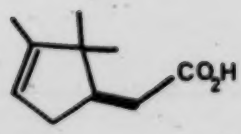

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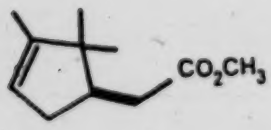

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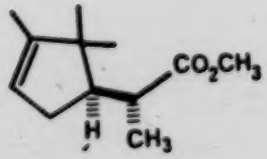

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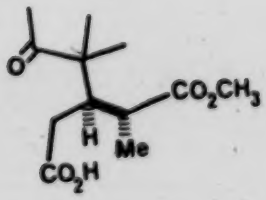
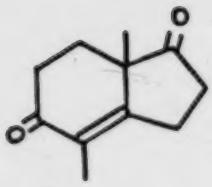


IX

The synthesis of the CD fragment III proved to be a difficult task. The preparation of III (R = Bn) was achieved as follows: diketone X was chemoselectively ketalized using 3-bromo-1,2-propanediol in the presence of p-toluenesulfonic acid to give bromoketal XI as a mixture of epimers. Reduction of XI with sodium boohydride in methanol and subsequent protection of the resulting allylic alcohol with benzyl bromide afforded ketal XII. Without purification, compound XII was hydrolyzed to ketone XIII under carefully controlled conditions. The formation of the bicyclo[4.4.0]decanolide portion of III from ketone XIII was accomplished in the following manner. Thiocarbomethoxylation of the ketone functionality using S,S'-dimethyl dithiocarbonate and potassium hydride in hexamethylphosphoramide afforded the β-keto thioester XIV which was further oxidized with benzoyl peroxide in the presence of potassium hydride to compound XV. Thioester XV, which was produced as a single isomer, underwent smooth reduction with sodium borohydride, and subsequent exposure to lithium hydroxide in aqueous methanol gave triol XVI in good yield. The conversion of triol XVI to lactol XVII proceeded smoothly upon exposure to periodic acid in aqueous acetone. The incorporation of the furan ring into the latent aldehyde



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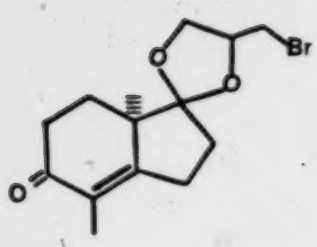

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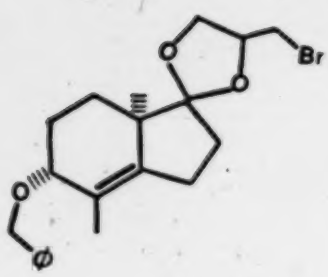

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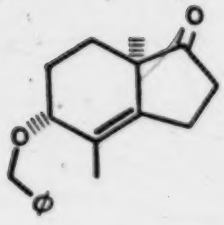

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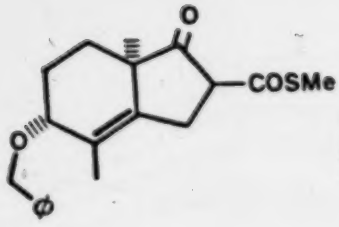

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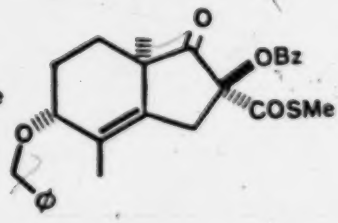

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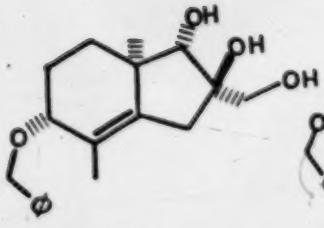

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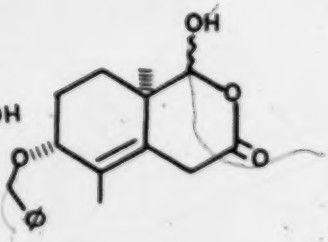

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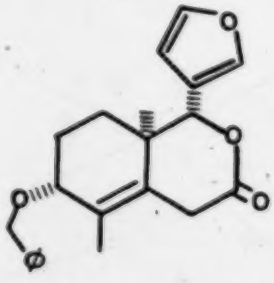

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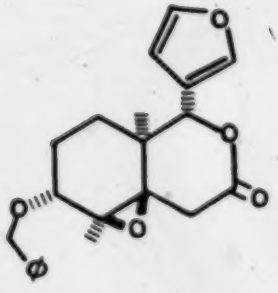

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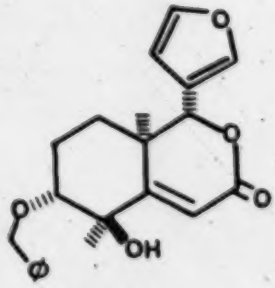

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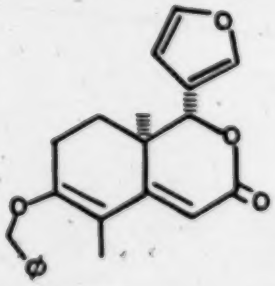

XXI

of **XVII** was found to take place under carefully defined conditions. The use of β-lithiofuran at room temperature was found to provide the best yield of lactone **XVIII**, which was produced as a single diastereomer. Epoxidation of **XVIII** with m-chloroperbenzoic acid afforded a single epoxide **XIX** which underwent rapid β-elimination on treatment with potassium t-butoxide to provide compound **XX** in respectable overall yield. Subsequent treatment of **XX** with thionyl chloride in pyridine finally gave the CD fragment **III** along with a small amount of its double bond isomer **XXI**. The coupling of diketo acid **II** and lactone **III** was attempted in a number of ways, and the results are discussed in detail.

Two additional routes toward the synthesis of mexicanolide were also examined. In the first, a Diels-Alder approach was explored as a means of achieving the stereoselective formation of the C4-C9 bond of mexicanolide. In the second approach, the coupling of a masked A ring with a C ring synthon was envisioned to provide a rapid access to the ABC portion of mexicanolide. The results of these studies are also presented in detail.

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It is a privilege for the author to express his gratitude to Prof. H.J. Liu for his support and outstanding supervision, even in those "difficult days". The author would also like to thank the staff of the microanalytical laboratory for the elemental analyses and to Dr. A.M. Hogg and associates for recording high resolution mass spectra on often almost imperceptible samples. The completion of this work would not have been possible without the expert assistance of the staff of the nmr laboratory: Dr. T.T. Nakashima, G. Bigam, L. Kong, G. Aarts and especially T. Brisbane. His good humour and interminable patience made the learning of the operation of the high field spectrometers a pleasure. I also would like to thank the Alberta Heritage Foundation for Medical Research for financial support, R. Swindlehurst and J. Hoyle for the FTIR spectra, J. Macaulay for proofreading the thesis and A. Wiseman for assuming the responsibility of typing the entire manuscript.

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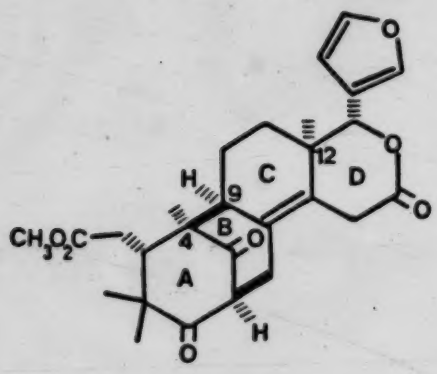
Studies on the Total Synthesis of Mexicanolide

INTRODUCTION

Mexicanolide (1), a modified triterpenoid of the limonoid family, was first isolated by Bevan and coworkers in 1963[1] from the species Cedrela odorata. It has since been found to occur in varying amounts in plants of the genera Khaya[2] and Xylocarpus.[3]

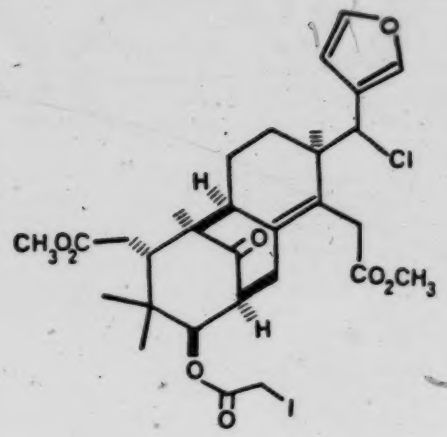


1

Due to mexicanolide's ready accessibility (up to 0.06% of dry plant)[1], structural studies began as early as 1965. The complete structure was elucidated by a combination of chemical transformations and spectroscopic analysis,[4,5] and was unequivocally confirmed by X-ray diffraction studies of derivative **2**,[6] prepared from mexicanolide in four steps.[7] Thus, treatment of **1** with methanolic sulfuric acid afforded methyl ether **3** which upon reduction with sodium borohydride gave one major alcohol, assigned structure **4**.[7] Esterification of **4** with chloroacetyl chloride and subsequent Finkelstein displacement of the chloride with iodide ion then furnished compound **2**.

In contrast to many other members of the limonoid family, the A and B rings of mexicanolide comprise a bicyclo[3.3.1]nonane system for which it has been subclassified as a bicyclononanolide. Over twenty bicyclononanolides have been isolated from natural sources. Some members of this group of compounds include swietenin (**5**),[8] xylocarpin (**6**)[9] and utilin (**7**).[10]

Due in part to its complicated architectural assembly, few studies have been undertaken toward the synthesis of mexicanolide. In this context, Connolly *et al.*[11] were able to manipulate 7-oxo-7-deacetoxy khivorin (**8**), an abundant naturally occurring limonoid, to


O
Cl
H
CH3O2C
O
CO2CH3
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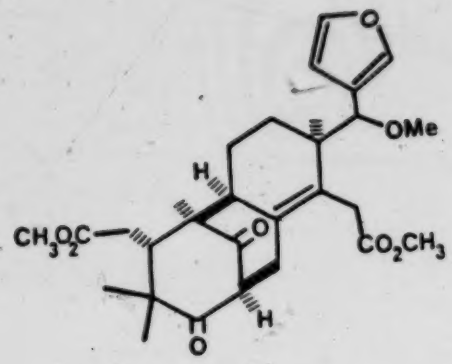
O
O
I

2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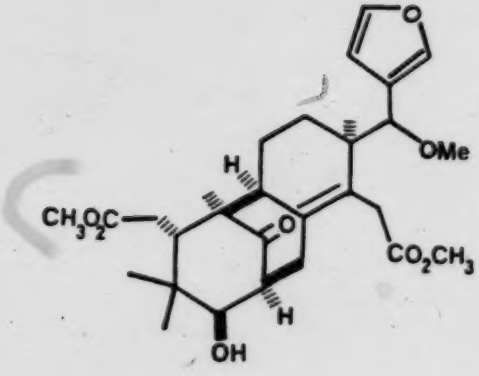
CH3O2C
O
CO2CH3
H
O

3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OH

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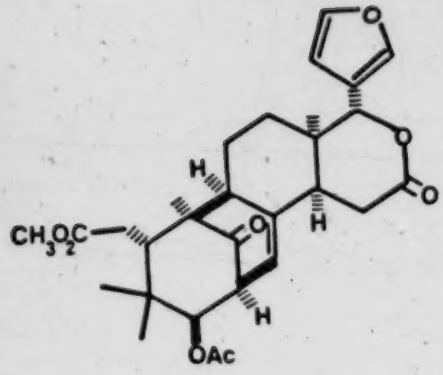
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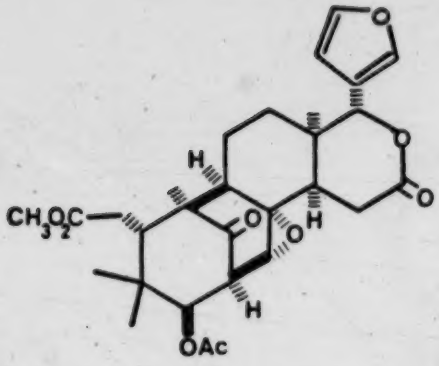
O
H
OAc

5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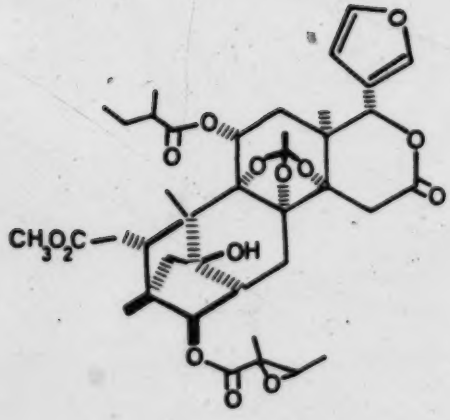
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O
CH3O2C
OH
O
O

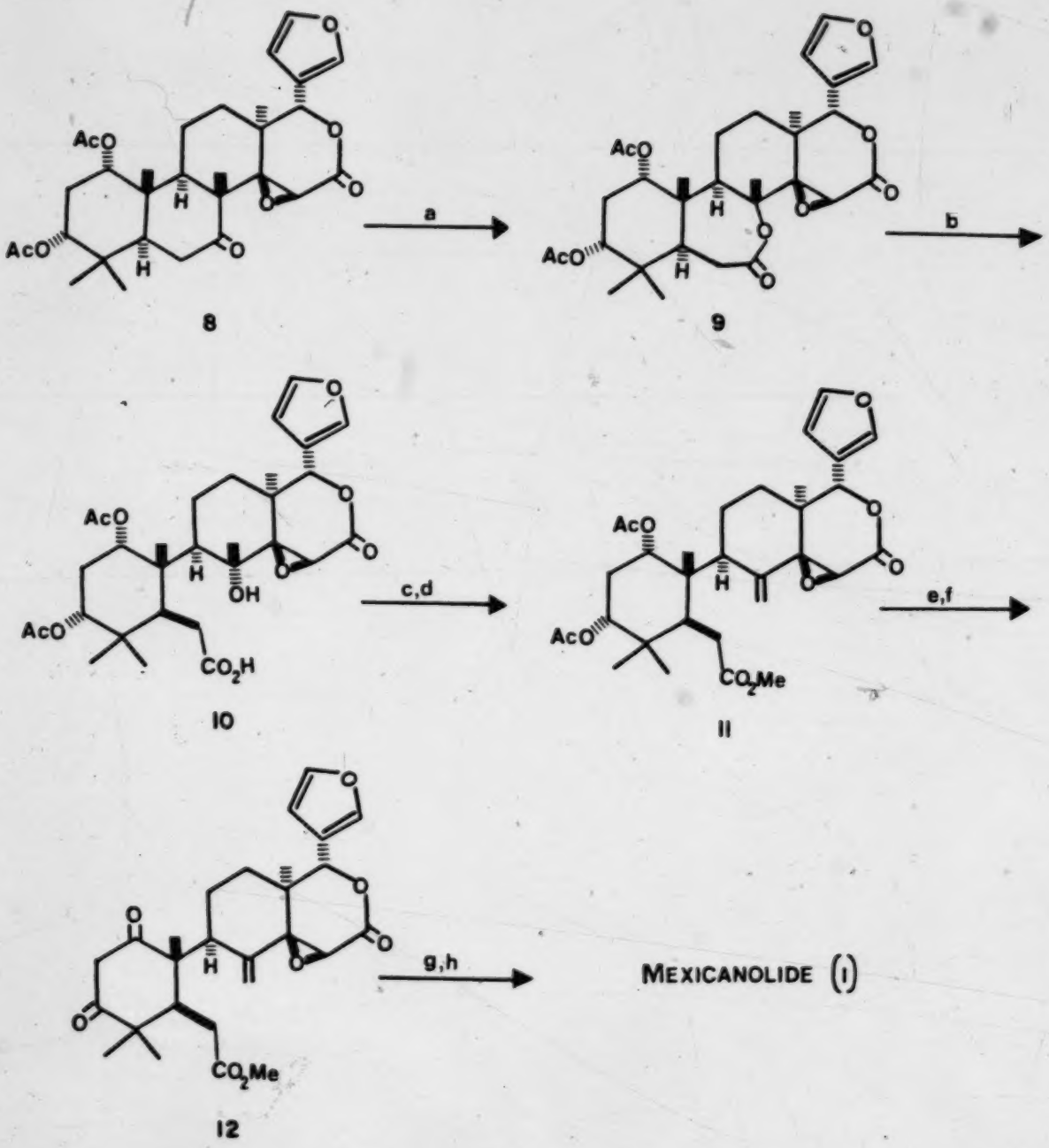
7

mexicanolide *via* the biomimetic sequence of reactions illustrated in Scheme 1.

Their approach capitalizes on the transposition of the bicyclo[4.4.0]decane system forming the A and B rings of **8** into the bicyclo[3.3.1]nonane portion of **1**. Conversion of **8** into dilactone **9** was effected by a Baeyer-Villiger rearrangement of the neopentyl ketone using peracetic acid. The seven-membered lactone ring of **9** underwent selective hydrolysis in the presence of "mild base"[11] to deliver acid **10**, which was esterified with diazomethane. The resulting alcohol was smoothly dehydrated to give olefin **11** upon treatment with thionyl chloride. Saponification of the two acetate groups of compound **11** followed by Jones oxidation of the resulting diol provided β-diketone **12**. Reductive removal of the epoxide ring using chromous chloride and subsequent base catalyzed intramolecular Michael addition of the 1,3-diketone moiety to the δ-carbon of the doubly unsaturated lactone system thus produced gave mexicanolide.

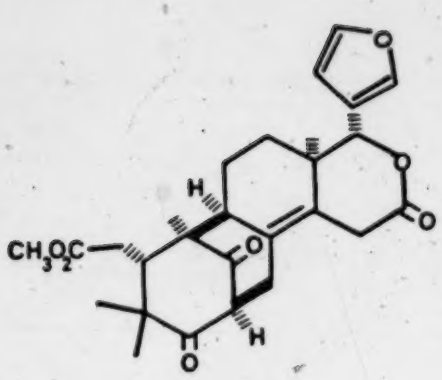
Attracted by the diverse array of functional groups embodied in mexicanolide and by its challenging molecular architecture, the bicyclo[3.3.1]nonane system in particular, we initiated a research program aimed at developing an efficient and convergent synthetic approach to this natural product.

Scheme 1



Conditions: [a] AcO_2H ; [b] mild base ; [c] CH_2N_2 ; [d] $SOCl_2$; [e] NaOH ; [f] Jones ; [g] $CrCl_2$; [h] aq. $NaHCO_3/CHCl_3$.

During the initial structural studies, mexicanolide was recognized as a considerably base-sensitive molecule, giving seco acid **13**, as a result of a 1,4-elimination reaction with concurrent scission of the bridgehead bond, upon brief treatment with dilute sodium hydroxide. This led us to consider the possibility of elaborating **1** *via* seco acid **13** by a 1,6-Michael addition, which would have the added advantage of taking place intramolecularly. In analogy with Connolly's observations, kinetic protonation of the resulting dienolate ion was expected to deliver the necessary tetrasubstituted double bond of mexicanolide. Appropriate conditions that would not elicit the reverse process will nevertheless have to be delineated. Further synthetic regression on compound **13** suggested that diketo acid **14** and diene lactone **15** could be regarded as potential synthons for the present purposes, since an intermolecular 1,6-conjugate addition of the β-diketone system of **14** to **15** with concomitant extrusion of the leaving group would deliver seco acid **13** in a completely regioselective manner. Evidently, unless optically pure intermediates are utilized, two diastereomeric adducts, namely **13** and **16**, may result from such a process, hereafter referred to as the A-CD approach.



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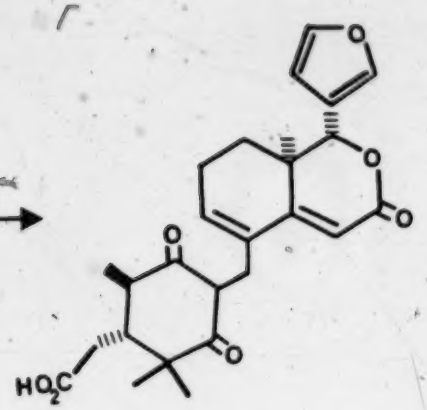
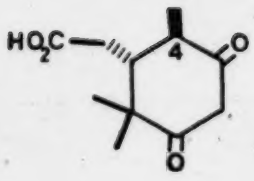
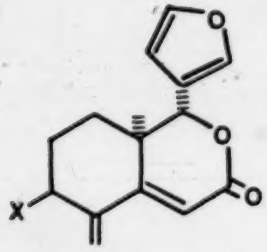


13

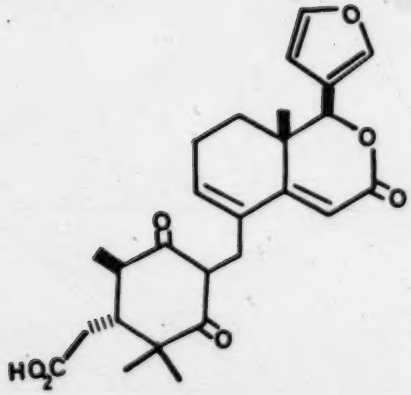


14



X= LEAVING GROUP

15



16

Two additional convergent strategies to the synthesis of **1** based on diketo acid **14** were also examined. In the first route, denominated the ACB approach, a Diels-Alder protocol was explored as a means to control the stereochemistry at C-4 and C-9 in **1** and to incorporate the necessary elements for further elaboration of the B and D rings. In the second scheme, the Michael addition of a masked A ring synthon to a C ring precursor was envisaged as a plausible solution to the formation of the critical bond linking C-4 and C-9 (mexicanolide numbering). In analogy with the ACB approach, this strategy also provides the appropriate functional groups to construct the B ring from an AC synthon. This route will hereafter be designated as the CAB approach. The results of our investigations in this area as well as the details of the stereoselective synthesis of compounds **14** and **15** shall be described in the next section.

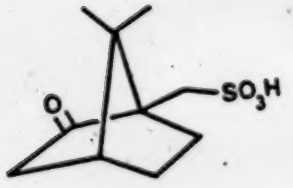
RESULTS AND DISCUSSION

1. The A Ring Synthesis

Two synthetic schemes were envisioned to provide diketo acid **14** in a simple fashion. Both utilize 10-camphorsulfonic acid **17** as starting material. Several features make this compound an attractive precursor of **14**. Firstly, it is readily available in very high optical purity, thus permitting the preparation of **14** in optically active form, and secondly, it possesses all but one of the carbon atoms required for the synthesis of **14**. In the present context, d-camphorsulfonic acid **17** was reacted with fused potassium hydroxide at ca. 400°C to provide (+)-campholenic acid **18**,[12] $[\alpha]_D$ = +8.1° ($CHCl_3$), in 51% yield. Compound **18** displayed a molecular ion peak at 168.1153 in the mass spectrum, consistent with the molecular formula $C_{10}H_{16}O_2$. Its infrared spectrum showed the presence of the carboxylic acid group at 3500-2300 and 1715 cm^{-1}, and in its ^1H nmr spectrum, three different methyl groups were observed at δ1.61 (vinylic), 1.02 and 0.81. These assignments were confirmed in the ^{13}C nmr spectrum, which in addition displayed the carbonyl carbon

at δ180.51 as a singlet. Also, a single set of peaks was observed in the high field ^{1}H nmr spectrum taken in conjunction with increasing amounts of europium tris-(2-trifluoroacetyl-d-camphorate), which suggested a very high optical purity.

The conversion of acid 18 into the methyl ester 19, $[\alpha]_D$ = +11.5° ($CHCl_3$), was effected in quantitative yield upon treatment with either methyl iodide or dimethyl sulfate in refluxing acetone containing suspended potassium carbonate. Compound 19 showed the ester carbonyl at 1740 cm^{-1} in the infrared spectrum and at δ173.86 in the ^{13}C nmr spectrum. In addition, the methoxy group was observed at δ3.68 as a singlet in the ^{1}H nmr spectrum.



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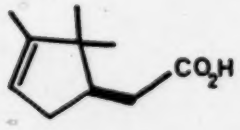

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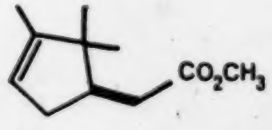

19

To confirm the optical purity of **18**, ester **19** was reduced to the corresponding alcohol **20**, $[\alpha]_D$ = +4.3° (CH_2Cl_2), in 90% yield using lithium aluminum hydride in ether. Alcohol **20** was then esterified in quantitative yield with (S)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (**21**) (pyridine, cat. dimethylaminopyridine,[13] room temperature), prepared from the corresponding carboxylic acid ((-)-Mosher's acid)[14] in 100% yield by treatment with oxalyl chloride in benzene containing a catalytic amount of dimethylformamide at room temperature. The resulting ester **22** was subsequently examined by 376 MHz ^{19}F nmr spectroscopy. A single peak was observed at δ42.3788 (relative to C_6F_6).* From this result it can be concluded that the enantiomeric excess of **18** is >99%. The same conclusion was arrived at by examination of the 400 MHz ^1H nmr spectrum of **22**, which displayed a single set of peaks. Along this line, it is interesting to note that the methoxy group appeared as a doublet (J = 2Hz) due to long range proton-fluorine coupling.

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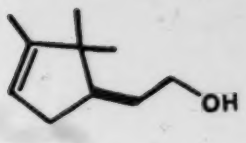
*A sample of the epimer of **22**, prepared from **21** and the enantiomer of **20**, displayed an ^{19}F signal at δ42.3578. The signals of the two diastereomeric esters were sufficiently well separated at this spectrometer frequency to permit individual assignments.



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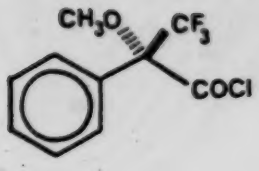

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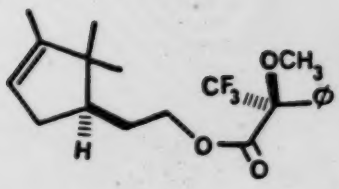
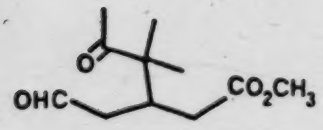


22

In an analogous manner, racemic 19 was prepared from d,l-camphorsulfonic acid. This material was used in the initial stages of the investigation toward the A ring synthesis.

In the first approach to β-diketone **14**, racemic **19** was subjected to ozonolysis in methylene chloride and methanol. The resulting ozonide was reduced with triphenylphosphine (-78°C → room temperature) to give the unstable keto aldehyde **23**. Compound **23** was not purified but cyclized directly to enone **24** in 61% yield from **19** via the agency of p-toluenesulfonic acid in refluxing benzene.



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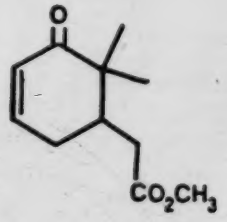
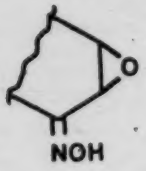


24

Corey's method for rearranging α,β-unsaturated ketones to β-nitro enones[15] was conceived as a plausible means to manipulate compound **24** to diketo acid **14**. This method involves the oxidation of epoxy oximes **25** to nitro alcohols **25a** by means of trifluoroperacetic acid followed by oxidation of the allylic alcohol moiety to the ketone **25b**. It was expected that the hypothetical enone **25c**

could be utilized to incorporate the required methyl group, and that the nitro olefin could deliver the β-diketone system upon reduction and hydrolysis.



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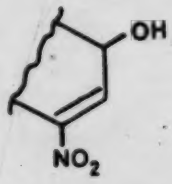
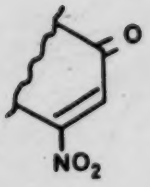
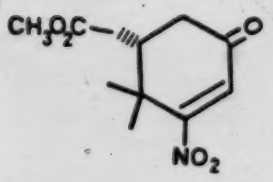


25a



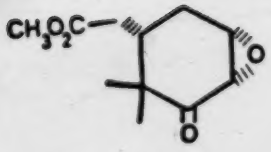
25b



25c

Toward this end, enone 24 was treated with 30% hydrogen peroxide in the presence of a catalytic amount of lithium hydroxide to give epoxy ketone 26 in 92% yield as a single diastereomer, as evidenced by the ^{1}H and ^{13}C nmr spectra, each of which displayed a single set of peaks. Its mass spectrum showed a molecular ion peak at 212.1042, consonant with the molecular formula $C_{11}H_{16}O_4$. In the ^{13}C

nmr spectrum, the ketone carbonyl was observed at δ208.45 and the ester carbonyl at δ172.85. In addition, the alpha and beta carbon atoms supporting the epoxide ring were observed at δ53.38 and δ45.52, respectively. The relative stereochemistry between the epoxide ring and the acetic ester side chain, which can be seen more clearly in structure **26a**, was derived from proton homonuclear decoupling experiments at 400 MHz, from which it was readily established that $J_{1,3}$ = 1 Hz, $J_{1,4}$ = 4 Hz, $J_{3,5}$ = 12 Hz and $J_{4,5}$ = 4 Hz. Thus H_3 must be <u>anti</u> with respect to both H_1 and H_5.



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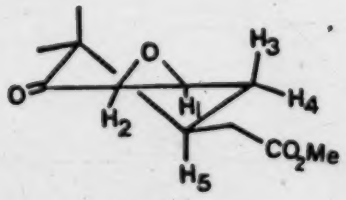
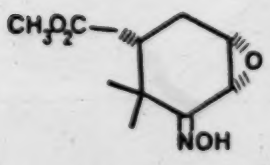
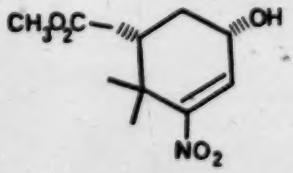


26a

Condensation of **26** with hydroxylamine hydrochloride in methanol furnished the expected epoxy oxime **27** in 84% yield after recrystallization. The presence of the oximino functionality was evident in the infrared spectrum, which showed a broad band at 3320 cm^{-1} and a sharp signal at 3600 cm^{-1}, assigned to the hydrogen-bonded and the free hydroxyl group, respectively. In addition, a molecular ion peak was observed at 227.1156 in the high resolution mass spectrum, which conforms to the molecular formula $C_{11}H_{17}NO_4$. In contrast to the literature claims,[15] exposure of compound **27** to trifluoroperacetic acid, prepared in acetonitrile solution from trifluoroacetic anhydride and 98% hydrogen peroxide, led to the recovery of the starting material. Very minor amounts of a number of by-products were also detected on TLC, but none displayed the structural features of the expected allylic alcohol **27a** according to ^1H nmr analysis.



27

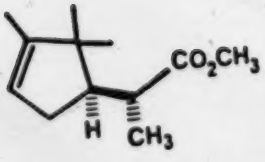


27a

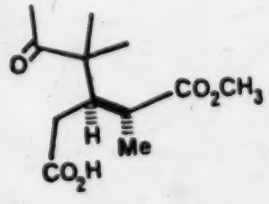
It should be noted that in order to prepare diketo acid **14** with the correct absolute stereochemistry at the carbon atom bearing the acetic acid side chain, it would be necessary to utilize l-camphorsulfonic acid, the least abundant antipode, as the starting material. As a result of this and of our inability to manipulate compound **27** to **14**, the present scheme was slightly modified.

In the second route to **14**, optically pure **19** was treated with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -76°C. When the resulting lithium enolate was exposed to methyl iodide, the corresponding monomethylated product **28**, $[\alpha]_D$ = -34.8° (CH_2Cl_2), was isolated in 86% yield as a single isomer displaying a single set of twelve lines in the ^{13}C nmr spectrum. Also, its mass spectrum showed a molecular ion peak at 196.1465 ($C_{12}H_{20}O_2$). In the ^1H nmr spectrum, a new methyl doublet (J = 7 Hz) appeared at δ1.16. Physical methods proved inefficacious at establishing the stereochemistry of the newly created asymmetric center. The assignment was made on the basis of subsequent chemical transformations. Compound **28** was found to be exceptionally resistant to dialkylation, even in the presence of excess base. When the purified ester **28** was resubjected to the treatment with LDA and methyl iodide,

no further alkylation occurred and **28** was recovered quantitatively. Addition of deuterium chloride in D_2O to the reaction mixture returned **28** in excellent yield. Thus, enolization of **28** is not taking place under this set of conditions. Ester **28** was treated with ozone in methylene chloride and methanol and the resulting ozonide was reduced with triphenylphosphine. Without purification, the keto aldehyde so produced was oxidized with Jones reagent to provide keto acid **29** in ca. 78% overall yield from **28**. The compound thus obtained was found to be contaminated by approximately 3% of triphenylphosphine oxide. This was, however, of no consequence as this impurity could be efficiently removed in the next step.



28

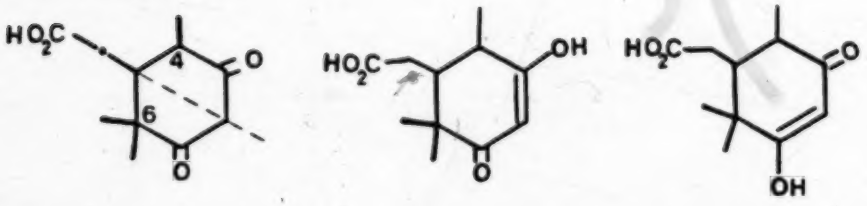


29

Exposure of keto acid **29** to an excess of lithium t-butoxide in refluxing 1,2-dimethoxyethane (DME) led cleanly to the formation of compound **14**, $[\alpha]_D$ = +57.8° (MeOH), with an efficiency of 56%. Racemic **14** could similarly be prepared from racemic **19** in comparable yields. Other bases such as sodium hydride in THF gave only partial conversions, at best. Examination of the ^{13}C nmr spectrum revealed that **14** was formed as a single diastereomer. Decoupling the methyl group of **14** at δ1.61 in the ^{1}H nmr spectrum caused the adjacent methine proton to collapse to a clean doublet. The coupling constant of 12 Hz provides irrefutable evidence that the relative stereochemistry between the secondary methyl group and the acetic acid side chain is trans.[16] Since ester **28** could not be forced to undergo enolization with a strong base such as LDA, it is highly unlikely that a complete epimerization of the carbon atom supporting the ester moiety has taken place during the Claisen condensation, which involves a weaker base. Thus, the configuration of that particular carbon must be the same in **28** and in **14**. It is worth mentioning that, at least in solution, the 1,3-diketone portion of **14** exists entirely in the enol form. This was most evident in its ^{1}H nmr spectrum (C_5D_5N) which displayed a singlet at δ5.77 corresponding

to the vinylic proton of the enol. Also, a doublet at δ102.24 was detected in the ^{13}C nmr spectrum, analogously ascribed to the vinylic methine carbon of the enol form. The direction of enolization was found to be solvent dependent. In methanol or pyridine solution, a unique set of signals was revealed in the ^{1}H nmr spectrum, whereas in acetone two sets were discernible, apparently due to the presence of the two enol forms **14b** and **14c**. In the ^{13}C nmr spectrum recorded in pyridine-d5 solution, the quaternary carbon bearing the gem-dimethyl group resonated at δ42.56, while the methine carbon adjacent to one of the ketone groups was observed at δ46.06. These assignments were corroborated by spin-echo J-modulated nmr spectroscopy.[17] As can be seen in structure **14a**, except for the lack of a methyl group, the molecule displays C_2 symmetry along the axis shown. Thus, carbons 4 and 6 are expected to experience similar shielding tensors due to steric effects so that their individual chemical shifts reflect the degree and type of substitution. Should the molecule exist in either the β-diketone form or in the enol form **14b**, C-6 would, on the basis of the well documented effects of substitution on ^{13}C chemical shifts,[18] appear at lower fields than C-4. This is, however, not the case. It is well established that a

ketone substituent induces larger downfield shifts in ^{13}C nmr spectra than olefinic substituents.[18] Therefore, the only way to accommodate the observed chemical shifts for C-4 and C-6 is by placing the ketone group of the enol form directly attached to C-4, as depicted in structure **14c**. The reasons for this particular preference are nevertheless not clearly understood.

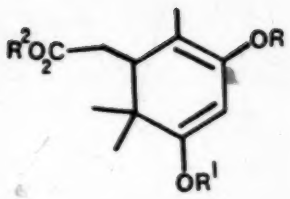


14a **14b** **14c**

2. The ACB Approach

With ample quantities of compound **14** available, its further transformation to the ACB portion of mexicanolide was examined. It was envisioned at this stage that a Diels-Alder reaction might provide the necessary elements for stereochemical control as well as the appropriate functional groups for an efficient AC-B ring closure.

The expectations were that if it were possible to prepare diene **30** from **14**, then a Diels-Alder reaction using 2-carbomethoxy-2-cyclohexenone (**31**) as the dienophile, which is known to provide *endo* adducts preponderantly with respect to the ester functionality,[19] would give bicyclic adduct **32** as the major product. Subsequent cleavage as shown by the arrows would deliver the AC portion **33** where the relative stereochemistry at all the asymmetric centers relevant to the natural product has been adequately controlled. The β-keto ester functionality of ring C (mexicanolide designation) in turn could be modified to enone **34** *via* a Mannich reaction. Closure of the B ring would then be effected by Michael addition of the β-diketone moiety to the exocyclic methylene carbon of the enone system giving compound **35**. The stereochemistry of the secondary bridgehead carbon would be dictated by that of the quaternary bridgehead carbon, and the resulting ketone on the C ring could in principle be utilized later on to incorporate the remaining methyl group and the D ring. It should be noted that the R and R' groups in diene **30** must be different in order to allow a regioselective cleavage of adduct **32**. Moreover, R' should be sufficiently stable to survive the Mannich reaction to be performed on the β-keto ester moiety of **33**.



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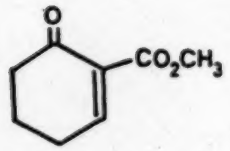

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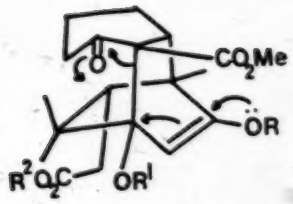

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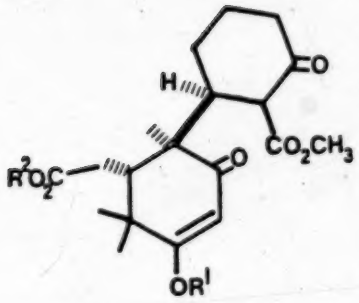

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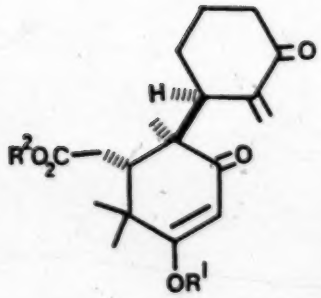

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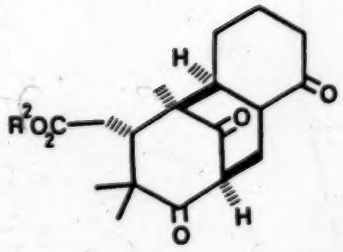
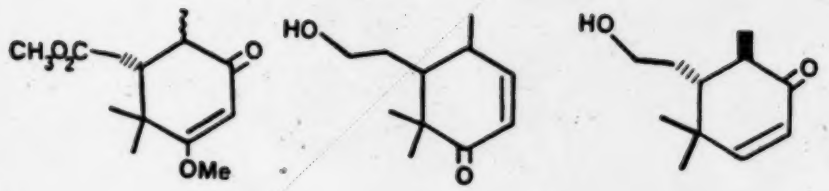


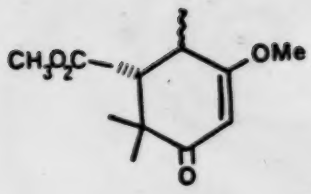
35

Bearing this idea in mind, racemic **14** was treated briefly with trimethyl orthoformate in methanol using sulfuric acid as catalyst and gave vinylogous ester **36** in quantitative yield. A single regioisomer was obtained, itself as a mixture of two stereoisomers in ca. equal amounts. The regiochemistry of compound **36** was unambiguously determined by reduction with lithium aluminum hydride followed by acid hydrolysis. Enone **37** was thus obtained as a single epimer. A number of minor secondary products were also observed on TLC, which could not be purified readily. Thus, the formation of the other diastereomer of **37** cannot be excluded. In the 200 MHz nmr spectrum of **37**, the alpha and beta protons of the enone system displayed long range and vicinal couplings of 3 Hz and 2 Hz, respectively, with the adjacent methine proton. Such splitting would not have been observed in the case of the regioisomeric enone **38**. The relative stereochemistry of **37** could not be ascertained from the ^{1}H nmr spectrum.



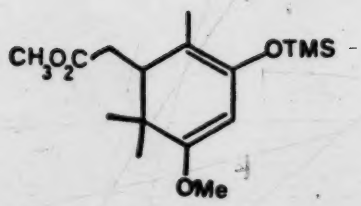
36 **37** **38**

Interestingly, when racemic **14** was treated with sulfuric acid in methanol in the absence of trimethyl orthoformate, two regioisomeric esters **36** and **39** were obtained in a 1:2 ratio, each also as a mixture of diastereomers in approximately equal amounts. The regiochemistry of these compounds was individually established again by reduction with lithium aluminum hydride followed by acid hydrolysis. In this fashion, **39** delivered enone **38** as the major product of which the alpha and beta vinylic protons appeared in the nmr spectrum as sharp doublets at δ5.83 and 6.59. The methine proton adjacent to the ketone group was observed as a doublet of quartets with coupling constants of 13 and 7 Hz, indicating a <u>trans</u> relationship between the ester side chain and the methyl group.



39

Upon exposure of a solution of ester **36** in triethylamine to an excess of trimethylsilyl trifluoromethanesulfonate, prepared from trimethylsilyl chloride and trifluoromethanesulfonic acid,[20] the corresponding diene **40** was produced in 100% yield. This result unequivocally confirmed that **36** is a mixture of stereoisomers and not regioisomers. Evidence for the structure **40** was derived from the ^{1}H nmr spectrum, which showed a singlet at δ0.15 integrating for nine hydrogens due to the trimethylsilyl group. In addition, a vinylic methyl group was observed at δ1.59 as a sharp singlet. In the infrared spectrum, two vinyl ether bands were observed at 1660 and 1609 cm^{-1}.



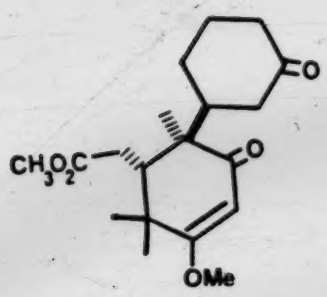
40

Model Diels-Alder reactions using 1,4-benzoquinone or maleic anhydride and diene **40** were very disappointing. Thermal reactions conducted at temperatures of up to 287°C in solvents such as p-cymene and n-hexadecane met with absolutely no success. Extensive decomposition was noticed in all cases. Attempted catalysis via Lewis acids such as $BF_3 \cdot OEt_2$ and $SnCl_4$ afforded only ester **36** as a result of hydrolysis, and polymerization products, respectively. Therefore, it may be concluded that steric congestion around the periphery of the six-membered ring of **40** effectively inhibits the approach of the dienophile. Electronic effects cannot be responsible for the lack of reactivity since Danishefsky has shown[21] that similar acyclic dienes

participate efficiently in [4+2] cycloadditions with a number of less activated dienophiles.

Being incapable of eliciting the desired cycloaddition reaction, attention was then turned to direct alkylation of the enolate ion derived from ketone **36** to create the quaternary asymmetric center and to append simultaneously the C ring of mexicanolide. Steric and electronic[22] effects were expected to control the approach of the electrophile in such a way that alkylation would proceed in an anti fashion with respect to the acetic ester side chain of the enolate.

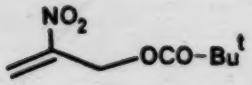
Pursuing this idea in the expectation of obtaining ketone **41**, a potential intermediate for the present purposes, silyl enol ether **40** was reacted with 2-cyclohexenone in the presence of titanium tetrachloride as described by Mukaiyama.[23] Here too, only ester **36** was obtained quantitatively. The use of trimethylsilyl trifluoromethanesulfonate as catalyst[20,23] was also of no avail. Even the reactive acrolein diethyl acetal prepared from acrolein and triethyl orthoformate using ammonium nitrate as acid catalyst,[24] failed to alkylate **40** in the presence of titanium tetrachloride.



41

Direct access to the ketone enolate of 36 was thwarted by the inability of strong bases such as lithium diisopropylamide, sodium hydride or potassium hydride in the presence of 18-crown-6 to elicit the desired deprotonation. Moreover, reaction of 36 with potassium hydride and 18-crown-6 followed by the addition of deuterium chloride in D_2O led to no deuterium incorporation as evidenced by ^1H nmr spectroscopy. Alternatively, diene 40 was treated with methyllithium[25] and the resulting enolate was exposed to a variety of

reactive electrophiles, including allyl bromide and nitro olefin **42**.[26] In these cases also, no carbon-carbon bond formation ensued.



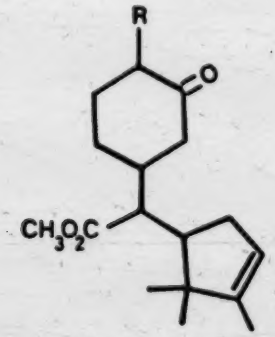
42

In view of our inability to effectively alkylate C-4 of diketo acid **14** or derivatives thereof, this line of investigation was not pursued further.

3. The CAB Approach

Attention was then focussed on the possibility of installing the C ring and the required methyl group onto ester **19** before unmasking the 1,3-cyclohexanedione moiety in order to avoid the lack of reactivity encountered previously in the alkylation of **36**. In this context, the

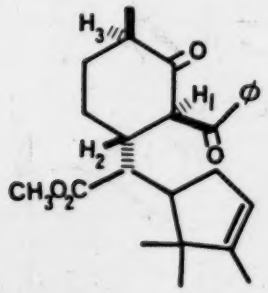
lithium enolate of racemic ester **19** was prepared in the usual manner with LDA. Addition of 2-cyclohexenone at -78°C and warming to room temperature resulted in the formation of Michael adduct **43** as an inseparable mixture of isomers in 79% yield. According to the ^{1}H nmr spectrum (100 MHz), four isomers were formed, one in considerable preponderance over the others. This reaction was equally successful with 6-methyl-2-cyclohexenone, synthesized from o-methylanisole by Birch reduction and acid hydrolysis, which already incorporates the C-12 methyl group of mexicanolide, to give adduct **44** in comparable yields (79%), also as an inseparable mixture of epimers.



43 (R= H)
44 (R=CH_3)

In order to alkylate the ester group of **44**, it became necessary to protect the ketone functionality. To do this, benzoyl chloride was added after the Michael addition in order to trap the resulting ketone enolate as the enol benzoate. The reaction was not clean, but a crystalline solid could be separated by fractional crystallization in 28% yield. Its mass spectrum depicted a molecular ion peak at 396.2296 corresponding to the expected formula $C_{25}H_{32}O_4$. However, three carbonyl absorption bands at 1738, 1708 and 1679 cm^{-1} were observed in the ir spectrum. Also, the ^{13}C nmr spectrum showed three singlets at δ208.91, 197.70 and 174.42. These spectral data clearly indicate that C-acylation rather than O-acylation had taken place to furnish compound **45**. By first order analysis of the ^1H nmr spectrum, the coupling constant between H_1 and H_2 was found to be 13 Hz which agrees with a <u>trans</u> relationship between them. Furthermore, decoupling the methyl group adjacent to H_3 caused this proton to collapse to a doublet of doublets (J_1 = 15 and J_2 = 6 Hz) due to coupling with the adjacent diastereotopic methylene protons. The large value of J_1 indicates that H_3 is disposed in an axial orientation and, by inferrence, the methyl group is equatorial. The relative stereochemistry of the two remaining chiral

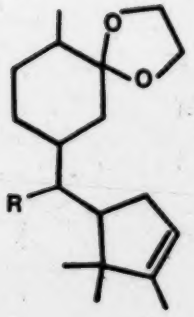
centers could not be established with certainty. An inseparable epimer of **45**, comprising ca. 13% of the total mixture, was also discernible in the ^{1}H and ^{13}C nmr spectra of **45**.

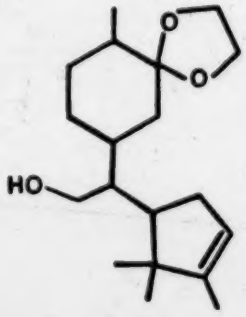


45

Compound **45**, still having a free ketone group, was not serviceable for the present purposes, so adduct **44** was ketalized using ethylene glycol and camphorsulfonic acid in benzene to provide ketal **46** in 100% yield. Attempted alkylation of **46** under a variety of basic conditions, including LDA/CH_3I, LDA/CH_3OSO_2F or LDA/CH_3OSO_2F/tetramethylethylenediamine (TMEDA) led to the complete recovery

of the starting material. Suspecting that the methine proton alpha to the ester had a relatively low acidity, the ester group of **46** was transformed into aldehyde **48** in 98% overall yield *via* a two-step sequence involving reduction with lithium aluminum hydride followed by pyridinium chlorochromate oxidation[27] of the resulting alcohol **47**. In the ^1H nmr spectrum compound **48** displayed four partially overlapping aldehyde singlets centered at δ9.84. Its mass spectrum revealed a parent ion peak at 306.2185, consistent with the formula $C_{19}H_{30}O_3$.

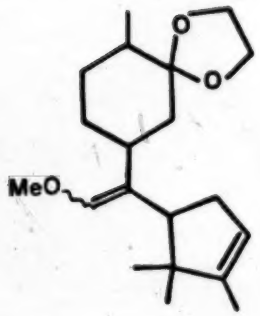




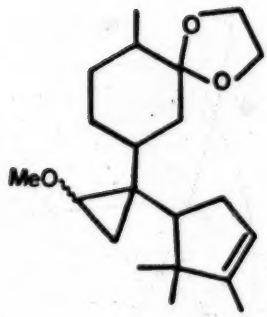
46 (R=CO_2CH_3) **47**

48 (R=CHO)

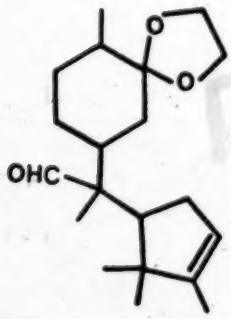
In analogy to ester **46**, compound **48** resisted alkylation with methyl iodide in the presence of strong bases such as LDA, sodium hydride and lithium dimethylamide. With potassium hydride in dimethylformamide (DMF) on the other hand, a monomethylated product was formed in 89% yield. Characteristic signals for vinylic protons at δ5.92 and 5.79 were observed in the ^{1}H nmr spectrum along with a strong vinyl ether absorption at 1655 cm^{-1} in the ir spectrum confirmed the speculations that compound **49** was the product of the reaction. This substance was still useful, as a selective Simmons-Smith reaction[28] would give cyclopropyl methyl ether **50**, which would conceivably deliver α-methyl aldehyde **51** upon treatment with acid. Unfortunately, all attempts to bring about the desired cyclopropanation reaction using the Simmons-Smith reagent met with failure. No reaction was observed in all cases. Also, no cyclopropane ring formation ensued when a mixture of compound **49** and diazomethane was irradiated with a high pressure mercury lamp[29] or when the mixture was heated in the presence of $CuI \cdot P(OEt)_3$.[29] In both cases, the starting material was recovered unchanged.



49



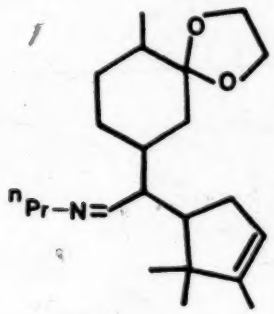
50



51

As a result of the above observations, it was not surprising to learn that the N-propyl imine 52, prepared from 48 in 73% yield by reaction with n-propylamine in

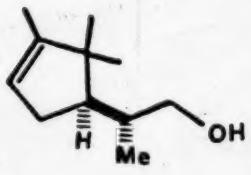
ethanol at 80°C, failed to give C-alkylation products when treated sequentially with potassium hydride in DMF or methyllithium in THF/hexamethylphosphoramide (HMPA) at room temperature and methyl iodide. The product of all these reactions was aldehyde **48** formed by hydrolysis of **52** during isolation. There was no reaction even with methyllithium in refluxing THF/HMPA.



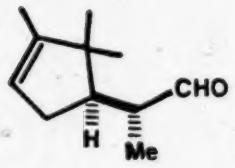
52

The dialkylation sequence was also examined in the reverse order. Since ester **28** had previously been found to be resistant to deprotonation, it was first converted into the corresponding aldehyde **54** in 88% overall yield by reduction with lithium aluminum hydride followed by oxidation of the resulting alcohol **53** with pyridinium chlorochromate.[27] That the stereochemical integrity was

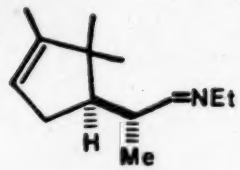
maintained during the transformations was apparent from the ^1H nmr spectrum of **54** which displayed only one set of signals, including a doublet at δ9.60 (J = 4 Hz) ascribed to the aldehydic proton. Also, the presence of the aldehyde group was most evident in the ir spectrum which showed a small absorption at 2699 cm^{-1} and a prominent band at 1720 cm^{-1}. Ethyl imine **55** was also prepared in quantitative yield by reacting aldehyde **54** with ethylamine and a catalytic amount of acetic acid at reflux for 1 hr. This compound displayed in the ^1H nmr spectrum the imino proton at δ7.51 as a doublet, J = 7 Hz, as well as a quartet at δ3.41, J = 7 Hz, assigned to the methylene group directly attached to the nitrogen atom. In analogy with compounds **48** and **52**, aldehyde **54** and its derivative **55** were recovered as a mixture of epimers when treated in succession with potassium hydride in DMF and 6-methyl-2-cyclohexenone.[30] Therefore, it appeared that by using the present methodology it was feasible to incorporate the C-4 methyl group or the C ring onto a masked A ring, but not both.



53

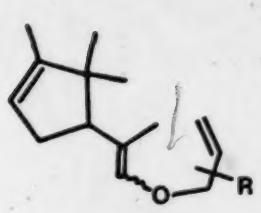


54

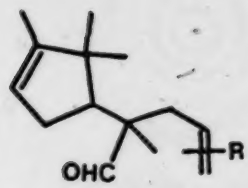


55

The observation that aldehyde **48** underwent clean O-methylation to give **49** led us to speculate that compound **54** might behave analogously. Moreover, if the alkylating agent were changed to an allylic halide, it should be possible to prepare 1,5-pentadiene **54a**. This compound in turn could provide aldehyde **54b**, which possesses a quaternary carbon alpha to the carbonyl, <u>via</u> a Claisen rearrangement.[31]

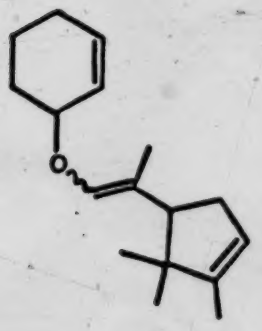


54a

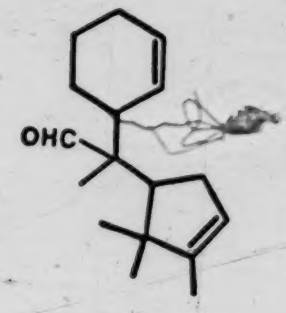


54b

With the intention of installing the C ring of mexicanolide using this strategy, compound **54** was treated with 3-bromocyclohexene in the presence of potassium hydride in DMF solution. Two alkylation products were isolated in 80% yield and in equal ratios and were identified as enol ether **56** and aldehyde **57**. Compounds **56** and **57** displayed nearly identical molecular ion peaks at 246.1983 and 246.1980, respectively, in agreement with the molecular formula $C_{17}H_{26}O$. The distinction was readily made by ^1H nmr spectroscopy, which showed two aldehydic singlets at δ9.98 and 9.86 in the case of **57**, and four vinylic protons in the case of **56**. Compound **56** was readily transformed into **57** in 80% yield by heating at 178°C in p-cymene solution via a Claisen rearrangement.[31]



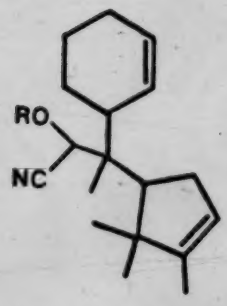
56



57

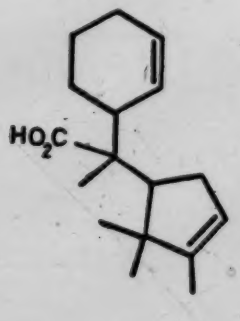
To continue the synthesis with 57, two manipulations need to be performed before unmasking the A ring. Firstly, the aldehyde must be converted to an ester and secondly, the olefin on the six-membered ring has to be transformed to a ketone. Toward the first goal, attempted oxidation of 57 with a variety of reagents including Jones reagent, Tollen's reagent and argentic oxide[32] afforded the starting material quantitatively. The conversion of 57 to 58 was accomplished by treatment with trimethylsilyl cyanide[33] in the presence of magnesium iodide in 91% yield. However, its further conversion to the carboxylic

acid 60 could not be effected using Jones reagent. A complex mixture of products was invariably obtained. Similarly, alcohol 59, obtained from 58 in 100% yield by treatment with fluoboric acid, also failed to give acid 60 when exposed to Jones reagent.



58 (R=TMS)

59 (R=H)

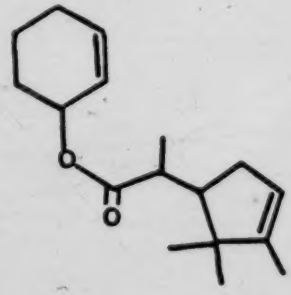


60

Toward the second goal, selective hydroboration of the disubstituted carbon-carbon double bond of 57 was envisioned as a means to introduce the ketone group necessary to functionalize the C ring. Not surprisingly,

reaction of **57** with borane-methyl sulfide led to reduction of both double bonds. Partial reduction of the aldehyde also occurred under these conditions. The use of dicyclohexylborane as the methyl sulfide complex also gave overreduction products. 9-BBN on the other hand, was found to be totally unreactive, even in refluxing THF.

In order to avoid the difficulties encountered during the oxidation of **57** to **60**, a slightly modified approach was undertaken. The idea was to attempt a Claisen rearrangement on ester **61** using Ireland's modification,[34] which involves the <u>in situ</u> generation and rearrangement of silicon ketene ketals.

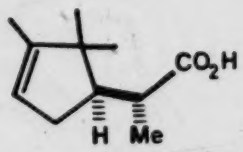


61

Toward this end, racemic ester **28** was saponified with lithium hydroxide in aqueous methanol. The resulting acid **62**, obtained in 98% yield, was esterified with 2-cyclohexene-1-ol prepared in quantitative yield by

reduction of 2-cyclohexenone with sodium borohydride in the presence of cerium trichloride.[35] The best coupling reagent was found to be phenyl dichlorophosphate in DMF,[36] giving **61** in 84% yield. Nevertheless, esterification *via* the corresponding acid chloride also proceeded satisfactorily (78%). In each case, a small amount (*ca.* 5-10%) of the corresponding anhydride of **62** was also formed. Compound **61** displayed in the ^1H nmr spectrum an AB system at δ6.00 and 5.76 characteristic of the *cis*-disubstituted olefin. The allylic proton on the carbon supporting the ester oxygen was shifted sufficiently downfield to overlap with the other vinylic proton at δ5.32. In addition, its mass spectrum showed a molecular ion at 262.1931, consonant with the formula $C_{17}H_{26}O_2$. Very disappointingly, compound **61** was recovered quantitatively when treated in succession with LDA and chlorotrimethylsilane as described by Ireland.[34] Attempted deprotonation with *sec*-butyllithium and TMEDA followed by quenching with N-trimethylsilyl imidazole also failed to provide any of the expected rearranged acid **60**. In all cases the starting material was recovered quantitatively. Furthermore, reaction of **61** with LDA and trapping with deuterium chloride in D_2O led to no deuterium incorporation, which indicates that the enolate

ion did not form at all. Also, no reaction ensued when potassium hydride was used as base in the presence of 18-crown-6. In the latter case, however, enolate formation did occur as evidenced by the evolution of hydrogen noted during the reaction. Moreover, the recovered acid **62** formed by hydrolysis of **61** was found to be a mixture of epimers by ^1H nmr spectroscopy.



62

At this stage, careful consideration of the results presented above forced us to seek alternative synthetic approaches toward mexicanolide.

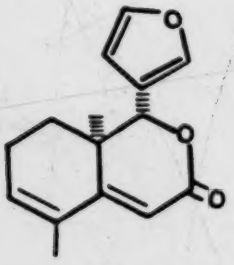
4. The A-CD Approach

So far, all the schemes examined have relied on the prior formation of the quaternary bridgehead bond of the B ring of mexicanolide as the key step. A highly convergent strategy, based on the Michael coupling of diketo acid **14** and diene lactone **15**, has now emerged as a viable route to seco acid **13**. Unlike the previous approaches, the prior coupling of the A ring with the CD fragment will allow the formation of the required bond linking C-4 and C-9 to take place intramolecularly.

a. Attempted construction of the CD fragment via bicyclic enone **65**

A literature search revealed that lactone **63**, an artificial product isolated from the pyrolysis of certain limonoids, had been prepared in 1973 by Tokoroyama and coworkers.[37] Their approach centered on the derivatization of 2,6-dimethylcyclohexanone **64** to the hexahydroindenone derivative **65** via alkylation with 2,3-dichloropropene in the presence of sodium hydride, hydrolysis of the resulting vinyl chloride with 90% sulfuric acid and condensation with methanolic potassium hydroxide. Enone **65** was in turn oxidized with lead tetraacetate in refluxing benzene to give α'-acetoxy enone **66** which without further purification was hydrolyzed to the corresponding ketol **67** upon treatment with potassium

carbonate in aqueous methanol in 74% yield. Exposure of compound 67 to lead tetraacetate in aqueous acetic acid resulted in the formation of lactol 68 in 94% yield as an epimeric mixture. Installation of the second double bond was accomplished by treatment of 68 with N-bromosuccinimide in $CHCl_3$-CCl_4 (1:1). The resulting diene 69 was then exposed to β-lithiofuran to furnish compound 63 and its epimer 70 in a 7:3 ratio.



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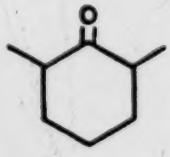

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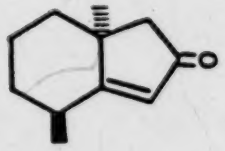

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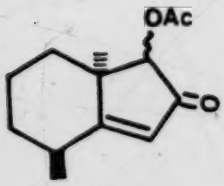

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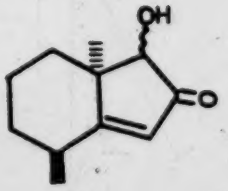

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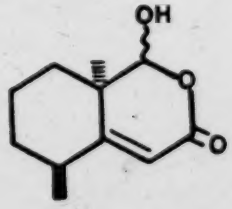

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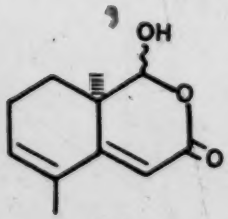

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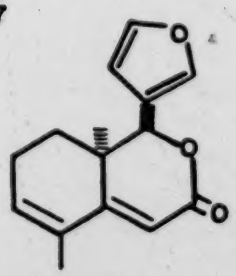
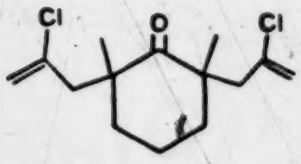


70

Our initial efforts concentrated on reproducing the above conditions in order to gain rapid access to 63, a plausible intermediate in the synthesis of 15. In our hands, the alkylation of 2,6-dimethylcyclohexanone with

2,3-dichloropropene did not proceed with sodium hydride in DME. The use of the corresponding allylic iodide (b.p. 45-60°C/20 torr), prepared in 42% yield by Finkelstein substitution of the chloride using potassium iodide in refluxing acetone for 3 hr, afforded considerable amounts of the dialkylated product **71** as a mixture of epimers. This shortcoming was alleviated by performing the alkylation reaction on keto ester **72** (b.p. 94°C/4 torr), prepared from 2-methylcyclohexanone in 81% overall yield by a two-step protocol involving carbomethoxylation with dimethyl carbonate in the presence of sodium hydride in DME and in situ alkylation of the resulting sodium enolate with methyl iodide. Treatment of **72** with 3-iodo-2-chloropropene in the presence of potassium hydride in DMF gave vinyl chloride **73** in quantitative yield as a diastereomeric mixture. Hydrolysis and decarboxylation proceeded uneventfully with aqueous barium hydroxide in methanol or preferably with lithium hydroxide to furnish compound **74** in 43% yield, identical with the material reported by Tokoroyama. No improvement in the efficiency of this last transformation was procured when sodium chloride or sodium iodide in wet DMSO[38] was utilized.



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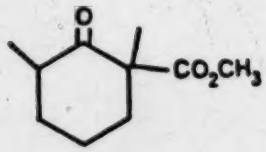

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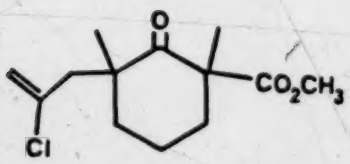

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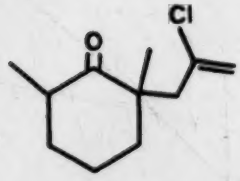
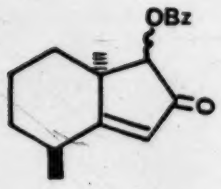


74

Further manipulation of **74** to **65** elicited no drawbacks and the subsequent steps were then examined. A variety of conditions were explored to foster the desired α'-acetoxylation reaction of enone **65**. The reported use[37] of lead tetraacetate in refluxing benzene yielded invariably complex mixtures of products. Kinetic enolate formation with LDA and concurrent trapping with benzoyl peroxide[39] failed to procure tangible amounts of the corresponding α'-benzoyloxy enone **75**. Frustrated by the lack of success in this area, we deemed it necessary to devise alternative solutions to the synthesis of **15**.



75

b. Attempted construction of the CD fragment through a Diels-Alder reaction

Inspired by Danishefsky's observations on the intermolecular Diels-Alder reaction of silyloxy dienes and conjugated aldehydes,[21] a synthetic scheme was developed which utilizes the [4+2] cycloaddition of diene **78*** and methacrolein as the key step in the construction of the six-membered carbocyclic ring of **63**. In this particular

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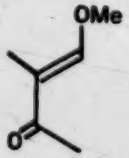
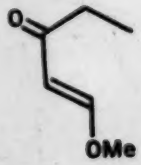
*Prepared in 66% yield (b.p. 65°C/0.06 torr) by treatment of 4-methoxy-3-methyl-3-butene-2-one (**76**) with LDA and subsequently with chlorotrimethylsilane. Compound **76** (b.p. 59°C/4.5 torr) was synthesized from methyl ethyl ketone by reaction with ethyl formate and metallic sodium in ether followed by O-alkylation with dimethyl sulfate in water.[40] Contrary to the literature claims, the other regioisomer **77** (b.p. 50°C/2.6 torr) was also obtained in comparable amounts and only a painstaking spinning band distillation succeeded in separating them.



76

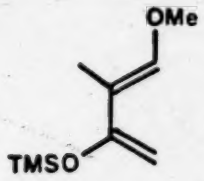


77

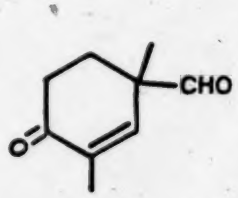
regard, when a benzene solution of **78** and freshly distilled methacrolein was heated at 120°C in a sealed tube for 20 hr and the resulting product stirred with aqueous fluoboric acid, the formyl ketone **79** was isolated in 49% yield after column chromatography. Compound **79** displayed the formyl proton as a sharp singlet at δ9.56 and the vinylic β-proton as a broad singlet at δ6.50 in the 200 MHz ^{1}H nmr spectrum. Its infrared spectrum showed the presence of a saturated aldehyde at 2718 cm^{-1} and 1720 cm^{-1} as well as an enone carbonyl at 1675 cm^{-1}. Further confirmation of the structure was derived from the ultraviolet spectrum in which two absorption maxima were observed at 257 nm (ε = 5384) and 306 nm (ε = 2370), ascribed to the $\pi\rightarrow\pi^*$ transition of the double bond and the $n\rightarrow\pi^*$ transition of the enone carbonyl, respectively. The reaction undoubtedly involves adduct **80** as an intermediate which collapses to **79** by elimination of the elements of methanol and fluorotrimethylsilane upon exposure to fluoboric acid. Always accompanying **79** in variable amounts was the methacrolein dimer **81** which could be readily separated by column chromatography.

Interestingly, both **79** and **81** displayed unexpectedly similar ^{1}H nmr and ir spectra so that structural assignments based on that type of information were not

feasible. However, only **79** showed a molecular ion at 152.0836 in the mass spectrum, consistent with the formula $C_9H_{12}O_2$. Moreover, **79** displayed in the ^{13}C nmr spectrum a doublet at δ200.54 and a singlet at δ197.91, assigned to the aldehyde and ketone carbonyls. Compound **81**, on the other hand, showed only a doublet at δ204.71.



78



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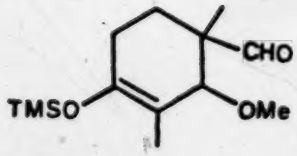
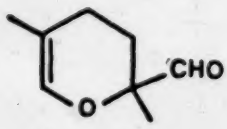


80



81

Addition of β-lithiofuran* to **79** at -78°C resulted in the formation of a complex mixture of products. The ^1H nmr spectrum of the mixture revealed the absence of vinylic protons in the 5-7 ppm region and of aldehydic protons. Also in its infrared spectrum no carbonyl absorption was observed below 1700 cm^{-1}. These data suggest that addition of the organometallic reagent to the aldehyde and 1,4 to the enone system was occurring under these conditions. This behaviour was found to persist irrespective of the conditions employed. This was somewhat disconcerting since α,β-unsaturated ketones show a marked propensity to undergo 1,2 addition with organolithium compounds. It thus appears reasonable to postulate that the conjugate addition is the result of the close proximity of a β-furyl anion to the β-carbon of the enone system, due to coordination with the lithium alkoxide engendered from the reaction of the aldehyde with

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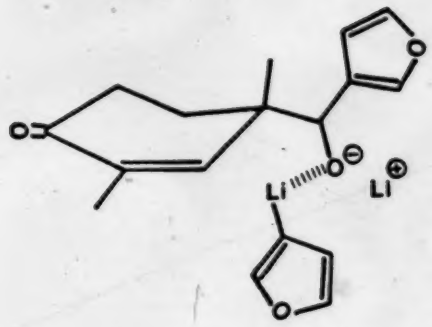
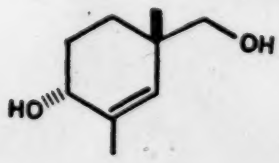
*Prepared by transmetallation of β-bromofuran with t-butyllithium in ether at -78°C. The use of THF in place of Et_2O gave rise to the competitive, and sometimes exclusive, α-deprotonation of the furan ring.[41] The use of n-butyllithium also gave mixtures of β-lithiofuran and 3-bromo-2-lithiofuran. β-Bromofuran was synthesized in two steps from the maleic anhydride-furan Diels-Alder adduct, namely bromination with bromine in chloroform followed by β-elimination and [4+2] cycloreversion in quinoline at 200°C.[42]

the organometallic reagent. This postulate is pictorially illustrated in structure 82.

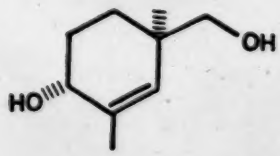


82

In order to avoid the above difficulties, attention was turned to installing the acetic acid portion of the heterocyclic ring of 63 prior to the reaction with β-lithiofuran. To accomplish this, compound 79 was reduced with diisobutylaluminum hydride in benzene to give two epimeric diols 83 and 84 in a combined yield of 72% and in a ratio of 2:1.

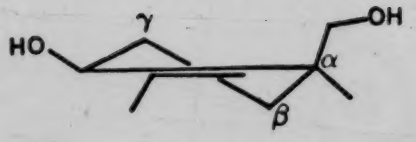


83



84

In the ^{1}H nmr spectrum of compound **83**, the allylic methine proton appeared at δ3.90, whereas the same proton in the trans diol **84** was observed at δ3.98. In addition, the methylene group of the primary alcohol was observed as a broad AB system (J = 11 Hz) at δ3.34 and δ3.25 in the trans isomer and at δ3.41 and δ3.31 in the cis isomer. Both compounds displayed very similar infrared spectra and molecular ions at 156.1150 and 156.1148 were observed in the mass spectra of the trans and cis isomers, respectively. The relative configurations of **83** and **84** were tentatively assigned by comparison of their ^{13}C nmr spectra. In the spectrum of the cis isomer **83**, the methylene carbon of the primary alcohol appeared at δ67.74, about 1 ppm further upfield than that in the trans isomer **84** (δ68.75). As can be seen in structure **85**, the aforementioned carbon experiences a γ-effect[18] with respect to one of the ring methylene carbons, due to which it is shifted upfield. Such steric interaction is absent in the trans isomer **84**, as depicted in structure **86**.

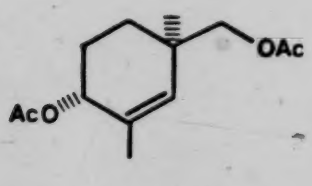


85

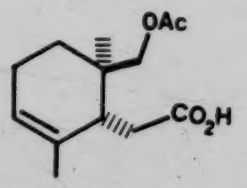
86

Ireland's modification[34] of the Claisen rearrangement was viewed as a logical alternative to introduce the acetic acid portion of **63**. For that purpose, it became necessary to prepare the diacetate of either **83** or **84**. It should be noted that only the allylic acetate would be capable of undergoing the rearrangement, so that selective protection procedures are unnecessary. Toward this end, the trans diol **84** was treated with acetic anhydride in pyridine containing a catalytic amount of dimethylaminopyridine to give the diacetate **87** in 81% yield. Better results were obtained when N-acetylimidazole in refluxing pyridine was used as the acetylating reagent, which gave **87** in quantitative yield. Attempted Claisen rearrangement of **87** however, afforded none of the expected transposed carboxylic acid

88, the diacetate being recovered unchanged. Thus, the neopentyl nature of the migrating terminus appears to be the culprit for the lack of reactivity.



87

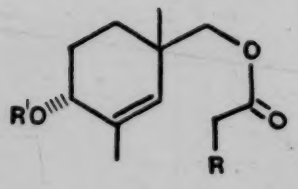


88

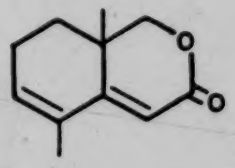
Analogous results were realized when 83 was refluxed in triethyl orthoacetate containing a catalytic amount of propionic acid,[44] although in this case variable amounts of the corresponding allylic propionate were isolated by chromatography. The use of 2,4-dinitrophenol or Amberlite IR-120 (H^+) as acid catalysts proved equally unsuccessful.

A plausible solution to the proper construction of the bicyclic portion of 63 derives from the hypothesis that a suitably functionalized acetate derivative 89 could be guided to undergo an S_N2 rearrangement via the enolate ion of the ester group. Ideally, the R group alpha to the primary ester would facilitate the ring closure by

increasing the acidity of the protons adjacent to the carbonyl and hopefully, would permit the introduction of the second double bond of **63** by some sort of elimination reaction. Along this line of reasoning, a phenylseleno group was deemed as the best candidate, as the selenium atom would certainly augment the rate of deprotonation and, once ring closure has occurred, oxidative elimination of the elements of phenylselenenic acid would give the expected diene **90**.



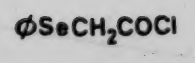
89



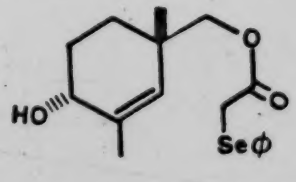
90

Toward this end, the <u>cis</u> diol **83** was esterified with phenylselenoacetyl chloride **91** (b.p. 120°C/0.7 torr), prepared from the corresponding carboxylic acid[45] by brief treatment with oxalyl chloride in refluxing benzene containing a catalytic amount of DMF. Very low levels of chemoselectivity were realized when N,N-dimethylaniline

was used as base, giving the desired monoester **92** in 13% yield at best. In the case of ethyl diisopropylamine, complex mixtures of products were invariably obtained, presumably as a result of ketene formation from the acid chloride **91**. The employment of collidine, on the other hand, afforded **92** reproducibly in 53% yield when the reaction was performed at -20°C in methylene chloride for 1.5 hr. Attempts were made to improve the yield of **92** by directly coupling phenylselenoacetic acid with **83** *via* the agency of carbonyldiimidazole[46] in pyridine or dicyclohexylcarbodiimide. Nevertheless, little selectivity was observed.



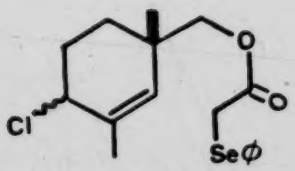
91



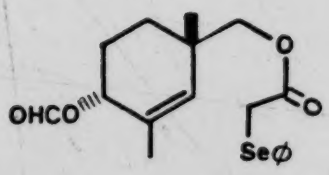
92

With compound **92** in hand, it was now necessary to transform the secondary allylic alcohol into a better leaving group in order to perform an S_N2 displacement.

The use of benzenesulfonic anhydride, prepared by dehydration of the corresponding acid with phosphorous pentoxide,[47] led to the complete recovery of **92**. The reaction of **92** with methanesulfonyl chloride in pyridine containing a crystal of dimethylaminopyridine afforded the allylic chloride **93** as an equimolar mixture of epimers in somewhat variable and modest yields. Very likely, the allylic mesylate, once formed, undergoes displacement by chloride ion. Compound **93** could be prepared with considerably higher efficiency (79%) by the reaction of **92** with oxalyl chloride in DMF. A single triplet for the two epimers was observed at δ4.35 in the 200 MHz ^{1}H nmr spectrum of **93** and was assigned to the allylic methine proton on the carbon supporting the chlorine atom. Apart from that, two sets of signals were clearly distinguished in the spectrum. The presence of the chlorine atom was firmly supported by mass spectral data, which revealed a cluster of molecular ions due to the presence of the six isotopes of selenium and the two of chlorine. The most abundant peak (^{80}Se, ^{35}Cl) was observed at 372.0387, which corresponds to the molecular formula $C_{17}H_{21}ClO_2Se$. Occasionally the formate ester **94** was also isolated in low yields.



93



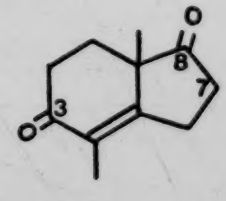
94

Very disappointingly, no cyclization ensued when chloride **93** was exposed to bases such as LDA in THF, sodium hydride in THF or 1,5-diazabicyclo[5.4.0]undec-5-ene in refluxing benzene. Without exception, a myriad of uncharacterizable products was formed. Consequently, this route to synthesizing diene lactone **63** via **79** was abandoned.

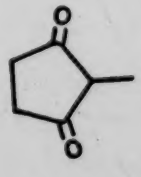
c. Stereoselective synthesis of diene lactones **15** and **63**

A more expedient approach to compounds **15** and **63** was envisioned which advocates the B ring fragmentation of some derivative of Wieland-Mischner ketone analog **95** to assemble the bicyclo[4.4.0]decanolide ring system in a simple fashion. For this purpose, 2-methylcyclopentane-1,3-dione (**96**)[48] was reacted with ethyl vinyl ketone in

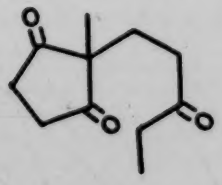
glyme solution using 1,4-diazabicyclo[2.2.2]octane as the basic catalyst to give the Michael adduct **97** in 100% isolated yield. Compound **97** displayed two carbonyl bands in the infrared spectrum at 1770 cm^{-1} and at 1715 cm^{-1}, assigned to the ring and side chain ketones, respectively. Exposure of **97** to p-toluenesulfonic acid or camphorsulfonic acid in refluxing toluene afforded ketone **95** in 98% overall yield. This represented a significant improvement over the previously reported syntheses of **95**, which claim overall efficiencies of 66%[49] and 51%.[50] Compound **95** displayed two bands in the infrared spectrum at 1738 cm^{-1} and 1650 cm^{-1}, characteristic of the five-membered ketone and the enone carbonyl, respectively. In addition, the vinylic and angular methyl groups were observed at δ1.83 and 1.36 in the ^1H nmr spectrum.



95



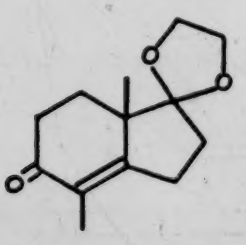
96



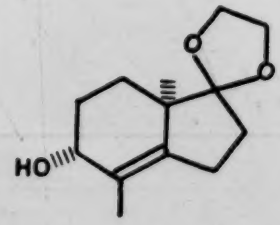
97

In order to be able to manipulate diketone **95** to **15** or **63**, the oxidation level at C-3, C-7 and C-8 must be adjusted accordingly. To this end, chemoselective protection of the saturated ketone as the ethylene ketal proceeded smoothly in the presence of ethylene glycol containing a catalytic amount of p-toluenesulfonic acid in refluxing benzene to furnish enone **98** in 91% yield after distillation. The regiochemical integrity of compound **98** was easily ascertained by infrared spectroscopy, which showed a single carbonyl absorption band at 1650 cm^{-1} due to the α,β-unsaturated ketone. Also, its mass spectrum revealed a molecular ion at 222.1258, consistent with the formula $C_{13}H_{18}O_3$. Reduction of the enone system with sodium borohydride in methanol (0° → room temperature) afforded in 74% yield, a single alcohol which was assigned structure **99**. Alternatively, the entire sequence can be performed in 79% overall yield from **96**, when the intermediate purifications are omitted. Compound **99** was considerably acid sensitive so that chromatography had to be performed on triethylamine-buffered silica gel. In its mass spectrum, alcohol **99** showed a molecular weight of 224.1414 consistent with the formula $C_{13}H_{20}O_3$. Furthermore, the presence of the secondary allylic alcohol moiety was easily established by the presence of a broad

triplet, J = 7 Hz, at δ4.14 in the ^{1}H nmr spectrum, ascribed to the allylic methine proton, and by the appearance of a doublet at δ71.43 in the ^{13}C nmr spectrum. Preliminary difference NOE experiments performed on compound **99** did not provide unambiguous stereochemical information. In this regard, irradiation of the angular methyl group caused no enhancement in the intensity of the proton on C-3. This result does not necessarily indicate that the hydroxyl and methyl groups are cis with respect to each other, as the proton on C-3 may be too far away from the angular methyl group to undergo a NOE enhancement due to T_1 relaxation of the latter. Nevertheless the stereochemistry depicted in structure **99** rests on spectroscopic analysis performed on a subsequent analog of this alcohol.



98



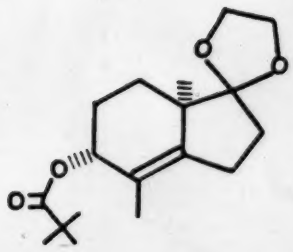
99

For further synthetic transformations, it was considered appropriate to protect the secondary alcohol function with a group capable of surviving mildly acidic and very basic (but not very nucleophilic) conditions that are necessary to adequately functionalize the five-membered ring. A pivalate ester was selected in this regard, as the carbon adjacent to the carbonyl is devoid of protons and thus is incapable of undergoing enolization. Also, the carbonyl group is of neopentyl type, thus reducing its propensity to undergo nucleophilic addition. The reaction of **99** with pivaloyl chloride in triethylamine in the presence of dimethylaminopyridine afforded none of the expected ester **100**, even at reflux temperature. In pyridine, however, the reaction proceeded exothermically to give **100** in 81% yield. Compound **100** showed the expected ester carbonyl bond at 1719 cm^{-1} in the infrared spectrum as well as the t-butyl group at 1390 cm^{-1}. As anticipated, the allylic methine proton and carbon underwent a downfield shift upon esterification to δ5.31 and δ73.72 in the ^{1}H and ^{13}C nmr spectra, respectively.

The hydrolysis of the ketal function of compound **100** under acidic conditions proved to be a very delicate reaction. Ketal **100** displayed an unexpected proclivity to

survive deketalization with either trifluoroacetic acid in aqueous acetone or with pyridinium p-toluenesulfonate in acetone.[51] The use of p-toluenesulfonic acid in acetone at 0°C did afford ketone **101**, although these maneuvers were not effectively reproducible. If this latter reaction is performed at room temperature, diene **102** can be isolated in 66% yield. The regiochemical outcome of the elimination reaction was readily proven by spectroscopic means. Thus in the ^{1}H nmr spectrum, compound **102** displayed the methylene protons adjacent to the carbonyl as an AB system, J = 24 Hz, at δ3.24 and 2.88. Also, two broad singlets in the vinylic region were observed at δ5.78 and 5.58, corresponding to the two olefinic protons. The use of concentrated hydrochloric acid in aqueous acetone (-12° → 20°C, 45 min) proved to be a vastly superior method to deblock the ketal function of **100**, giving **101** reproducibly in 79% yield. Purification by HPLC gave very pure material, although recrystallization from aqueous methanol was experimentally much more convenient. Alternatively, the esterification and hydrolysis reactions could be performed with an overall efficiency of 78% when the intermediate purification was omitted. Compound **101** displayed a strong carbonyl absorption band in the infrared spectrum at 1740

cm^{-1} assigned to the five-membered ketone. In addition, exact mass measurements revealed a molecular weight of 264.1726, in agreement with the formula $C_{16}H_{24}O_3$. Due to the simplicity of its 400 MHz ^1H nmr spectrum, ketone **101** was deemed an appropriate probe to carry out NOE studies aimed at determining the relative stereochemistry of the molecule. Toward this end, irradiation of either the methine proton on C-3 or the angular methyl group led to no enhancement in the intensity of any proton in the molecule. Suspecting that the NOE effects could be very small, the experiment was carried out in two dimensions using the NOESY pulse sequence $(90°\text{-}t_1\text{-}90°\text{-}t_m\text{-}90°\text{-FID})_{16x}$,[52] where t_m refers to the mixing delay time in which NOE exchange occurs. For this purpose, the spin lattice relaxation times were estimated from an inversion-recovery plot at 200 MHz. The t_m time was varied between ±50% of the T_1 of the angular methyl group (0.7 sec) and of the allylic methine proton (2 sec) in a set of ten experiments. In addition, t_m was varied systematically over 10-15% to suppress scalar correlation <u>via</u> J-coupling. Unfortunately, no long range NOE's could be detected in these experiments.



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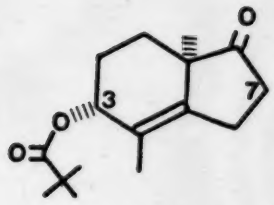

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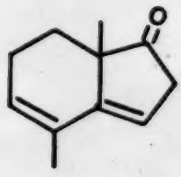
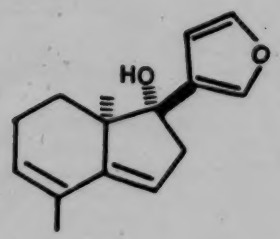


102

It should be recognized that compound **102** already encompasses the diene portion of **63** in the correct position. If it were possible to incorporate the β-furan ring and to cleave the five-membered ring at this stage, a short synthesis of **63** would be at hand. This aspect was briefly examined. Exposure of ketone **102** to β-lithiofuran in ether afforded adduct **103** in ca. 30% yield at 80% conversion. The use of a large excess of the organometallic reagent improved neither the yield nor the

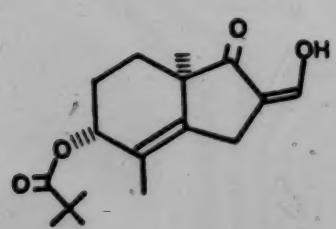
percent conversion. The recovery of some starting material makes it clear that competitive enolization of 102 is taking place under this set of conditions. The stereochemical assignment of 103 rests on well precedented analogous reactions in the steroid field in which the newly created hydroxyl group is cis-oriented with respect to the angular methyl group.[53] Being unable to improve the efficiency of this process, it was not pursued further.



103

Before proceeding with the cleavage of the five-membered ring of 101, the C-7 methylene carbon has to be oxidized to a ketone or equivalent functional group. This was attempted in the following manner. Reaction of 101 with ethyl formate in the presence of sodium hydride gave

the crystalline hydroxymethylene ketone **104** in 80% yield. According to ^1H nmr spectroscopy, the enol to keto aldehyde ratio of **104** was *ca.* 5:1. Attempted formation of the dithiospiro[5.4]decane system **105** *via* reaction of **104** with S,S'-bis-*p*-toluenesulfonyl-1,3-propanedithiol[54] using sodium acetate as the basic catalyst resulted in the complete recovery of the starting material **104**. The use of other bases such as lithium *t*-butoxide or lithium carbonate at temperatures of up to 100° had no effect. Similarly, no reaction was observed when the direct oxidation of the lithium enolate of **101** with $MoO_5 \cdot Py \cdot HMPA$[55] or benzoyl peroxide[39] was attempted, nor was it possible to trap such an enolate with chlorotrimethylsilane. The expected silyl enol ether **106** would have been a potential intermediate for the present purposes.



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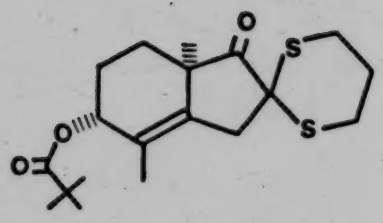

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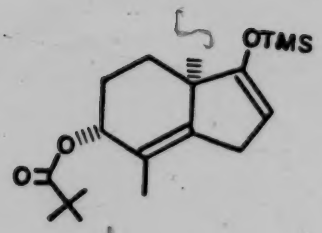
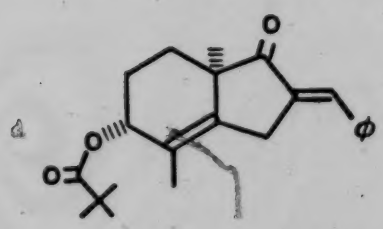


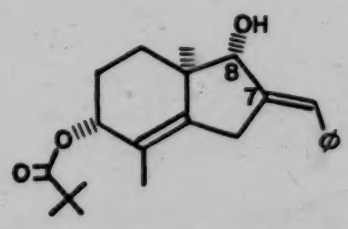
106

On treatment with benzaldehyde and sodium hydride in refluxing toluene, 101 gave enone 107 in 93% yield. Compound 107 displayed a molecular ion peak at 352.2028 in its mass spectrum, consistent with the expected formula $C_{23}H_{28}O_3$. In the ^1H nmr spectrum, it showed the bis-allylic methylene protons as an AB system (J = 17 Hz) at δ3.66 and 3.54 as well as six protons in the 7.1 to 7.7 ppm region, ascribed to the five aromatic protons and the enone β-proton. Moreover, the ketone carbonyl underwent

an upfield shift to δ208.13 in the ^{13}C nmr spectrum relative to **101** due to conjugation. Compound **107** was then reduced with sodium borohydride in the presence of cerium trichloride[35] to give regioselectively alcohol **108** in 100% yield. This compound was formed as a single isomer as shown by ^{13}C nmr spectroscopy, which displayed a single set of peaks, including a signal at δ73.64 assigned to the allylic methine carbon supporting the hydroxyl group. Also, its mass spectrum showed a molecular ion peak at 354.2188, corresponding to the molecular formula $C_{23}H_{30}O_3$. The configuration of the new allylic carbon was established on the basis of the 0.2 ppm upfield shift experienced by the angular methyl group when the solvent was changed from $CDCl_3$ to C_6D_6.[16]



107

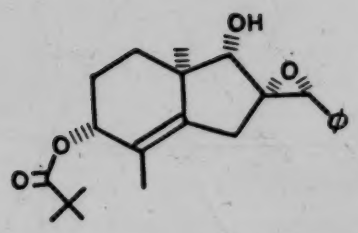


108

It should be noticed that compound **108** depicts the correct oxidation level at C-7 and C-8 necessary for its conversion to **63**. This was attempted as follows. Selective epoxidation of the conjugated double bond of **108** with t-butyl hydroperoxide in the presence of vanadyl acetoacetonate according to Sharpless[56] did afford epoxide **109**, but the reaction was capricious and could not be carried to completion. Also, when enone **107** was treated with t-butyl hydroperoxide in the presence of either Triton B or lithium hydroxide, very complex mixtures of products were always obtained, with perhaps only traces of the required epoxy ketone **110** being formed. Suspecting that the conjugated double bond of **108** was devoid of the necessary electron density to undergo selective epoxidation, the phenyl group was replaced by a methoxyl group. To this end, compound **104** was treated with dimethyl sulfate in the presence of triethylamine or sodium hydride to give compound **111** in ca. 20% yield. A dramatic increase in yield ensued when the reaction was performed under acidic conditions. Thus, the treatment of **104** with p-toluenesulfonic acid in dry methanol containing 3 Å molecular sieves led to the formation of **111** in quantitative yield. Compound **111** showed a singlet at δ3.89 in the ^{1}H nmr spectrum corresponding to the methoxyl

group of the vinylogous ester. This was corroborated in the ^{13}C nmr spectrum in which a signal at δ61.72 was observed. Reduction of **111** with sodium borohydride and cerium trichloride[35] furnished a single alcohol **112** in 88% yield as a very unstable oil. Attempted purification of **112** led to considerable decomposition. It was very disappointing to find that **112** underwent extensive decomposition when exposed to OsO_4/H_5IO_6, t-$BuO_2H/VO(acac)_2$, $MCPBA/CH_2Cl_2$ or $OsO_4/NaIO_4$, conditions that were expected to cleave the five-membered ring to produce lactol **113** or to provide intermediates for such cleavage. Consequently, the manipulation of **101** to **63** had to rely on less direct routes.

In this context, compound **101** was treated with an excess of dimethyl carbonate in the presence of sodium hydride in either THF or DME to provide β-keto ester **114** in 75-100% yield as an inseparable mixture of isomers. Reaction of the sodium enolate of **114**, generated in THF or DME with sodium hydride, with an excess of benzoyl peroxide[39] at -25°C gave triester **115** as a single epimer in 75% yield. Significantly lower efficiencies were realized when the conversion of **101** to **115** was attempted in one flask. The stereochemical homogeneity of **115** was evident from the ^1H (200 MHz) and ^{13}C (100.6 MHz) nmr



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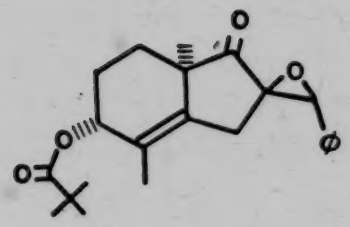

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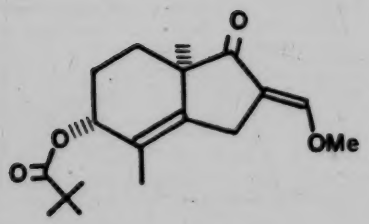
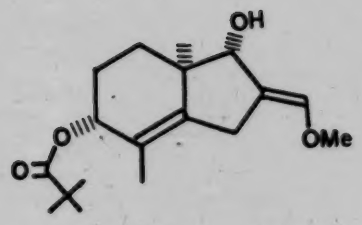
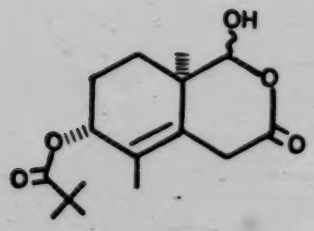


111

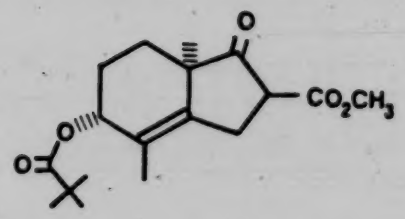


112



113

spectra, in which a unique set of signals was observed. Four singlets were observed in the ^{13}C nmr spectrum of 115 at δ208.67, 178.72, 168.02 and 165.01, assigned to the ketone, pivalate, carbomethoxy and benzoate carbonyls, respectively. Furthermore, high resolution mass spectrometry established the molecular formula as $C_{25}H_{30}O_7$ on the basis of the observed molecular weight of 442.1987. It was not possible to use spectroscopic methods profitably for stereochemical analysis of 115. The configuration shown was retrieved from subsequent chemical transformations.



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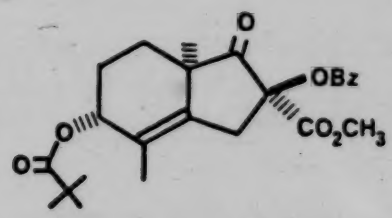
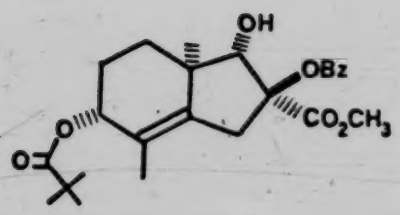


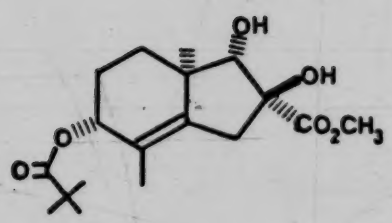
115

The ketone group of 115 was chemoselectively reduced to the alcohol level with sodium borohydride in methanol

in 100% yield. The homogeneity of compound **116** so produced was easily verified by ^{1}H and ^{13}C nmr spectroscopy. In this particular case, only three carbonyls were observed in the ^{13}C nmr spectrum at δ178.43 (pivalate), 170.46 (carbomethoxy) and 166.53 (benzoate). In addition, a doublet at δ73.28 was indicative of the presence of the secondary alcohol moiety. The stereochemistry at C-8 was tentatively assigned on the basis that irradiation of the methine proton at C-8 led to a +14% enhancement in the intensity of the hydroxyl proton, but to no enhancement of the angular methyl group. The benzoate group of **116** was chemoselectively cleaved with one equivalent of sodium methoxide in dry methanol to furnish diol **117** in 65% yield. That the hydrolysis had occurred in the anticipated sense was verified by the isolation of methyl benzoate from the reaction mixture, and by the presence of only two carbonyl signals in the ^{13}C nmr spectrum of **117** at δ178.48 (pivalate) and 174.83 (carbomethoxy). Prolonged exposure of **117** to sodium periodate led to the complete recovery of the starting material. This observation suggests that the two hydroxyl groups on C-7 and C-8 are <u>trans</u> with respect to each other.

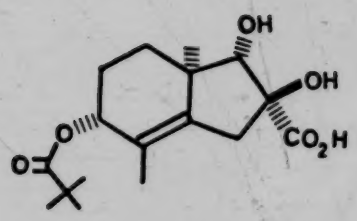


116



117

Subsequent reaction of 117 with one equivalent of lithium hydroxide in aqueous methanol at 60°C afforded the expected diol carboxylic acid 118 in 55% yield by direct crystallization. The regiochemical outcome of the reaction was unambiguously ascertained by the ^{13}C nmr spectrum, which was devoid of any absorption due to a methoxyl group. This was confirmed by ^{1}H nmr spectroscopy. In addition, the t-butyl group of the pivalate ester was clearly observed at 1394 cm^{-1} in the FTIR spectrum.

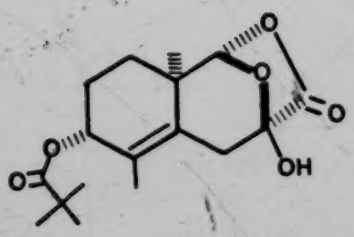


118

Having succeeded in adjusting the oxidation level at C-7 and C-8 to be the same as in **63**, the fragmentation of the five-membered ring was examined next. Exposure of **118** to an excess of periodic aid in aqueous acetone gave a single product according to TLC analysis. The molecular formula of $C_{17}H_{24}O_6$ calculated on the basis of high resolution mass spectrometry, indicated that this product still had the same number of carbon atoms as the starting material, suggesting that oxidation of the carboxyl group to CO_2 had not taken place as expected. Of particular structural diagnosis was the ir absorption at 1800 cm^{-1}, characteristic of a carbonyl group directly attached to an electron withdrawing substituent. In the ^{13}C nmr spectrum

a singlet and a doublet were observed at δ98.09 and 72.79, respectively. On the basis of the above data, structure **119** was proposed for this compound. It is worth mentioning that the angular methyl group underwent a ca. 0.4 ppm upfield shift when the solvent was changed from $CDCl_3$ to C_6D_6. This observation suggested that the bridge lactone was cis with respect to the angular methyl group. Further chemical proof for the structure was derived from the reduction of **119** with sodium borohydride and subsequent treatment with p-toluenesulfonic acid in methylene chloride. This protocol afforded a single α-hydroxyl actone **120**, whose stereochemistry was not elucidated. Thus, exclusive scission of the C7 - C8 bond was occurring during the oxidation process. Mechanistically, the formation of **119** can be visualized as proceeding by fragmentation of the initially formed complex **121** or **122** followed by intramolecular acetal formation, as illustrated in Scheme 2.

The use of tetramethylammonium or sodium periodate had no effect on the formation of **119**. Lead tetraacetate was examined extensively as an alternative to periodic acid. In a variety of solvents, including acetic acid, pyridine, aqueous acetic acid or aqueous pyridine, intractable mixtures of products were invariably formed.



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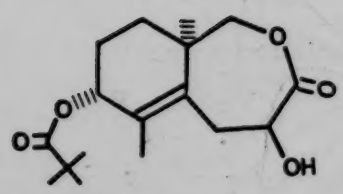
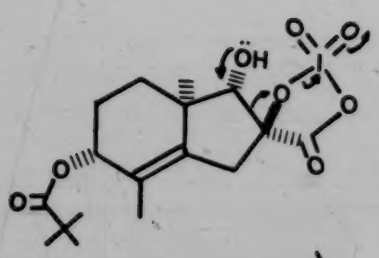
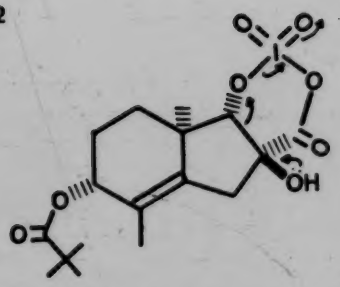


120

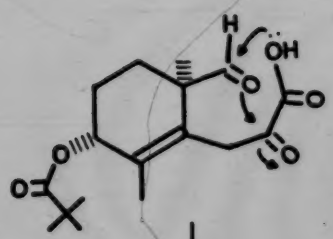
Scheme 2



121



122

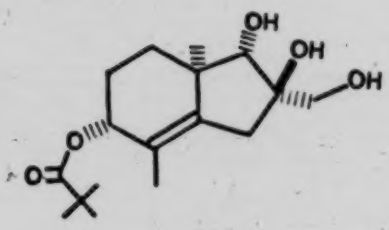


119

Similar behaviour was noticed with sodium bismuthate in acetic acid, which afforded none of the desired lactol **113**.

Since tricyclic lactone **119** was not serviceable for the synthesis of **63**, compound **118** was reduced with borane-methyl sulfide complex to the corresponding triol **123**. The efficiency of the reaction was only 21%, with the remaining 79% being lost apparently by concurrent hydroboration of the tetrasubstituted double bond. Triol **123** showed three hydroxyl protons in the 200 MHz ^1H nmr spectrum (DMSO-d6) at δ4.92 (doublet, J = 6 Hz), 4.42 (singlet) and 4.36 (triplet, J = 6 Hz) assigned to the secondary, tertiary and primary alcohol, respectively. Compound **123** underwent rapid oxidation when treated with periodic acid in aqueous methanol to provide aldehyde **124** in 62% yield. That fragmentation had indeed occurred was apparent from the ^1H nmr spectrum which showed the aldehyde proton at δ9.44 as a singlet and the methylene protons adjacent to the methyl ester as an AB system, J = 17 Hz, at δ3.14 and 3.00. The peak of highest mass in the mass spectrum of **124** appeared at 282.1818 ($C_{16}H_{26}O_4$) which corresponds to the loss of carbon monoxide from the molecule ($C_{17}H_{26}O_5$). Very likely, compound **124** arises by fragmentation of **124a** initiated by nucleophilic attack of

methanol to the ketone carbonyl. Contrary to expectations, compound **124** furnished a complex mixture of products when treated with β-lithiofuran. Chromatographic analysis failed to reveal the presence of even traces of the desired condensation product **125**. One is then led to believe that no discrimination between all the possible electrophilic centers in **124** is being made by the organometallic reagent.



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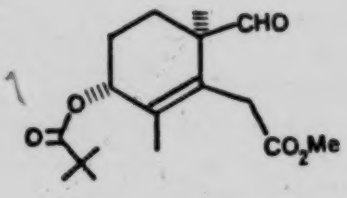
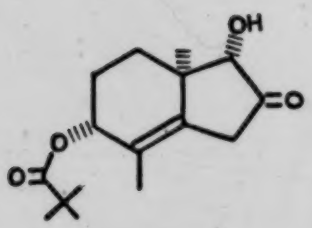
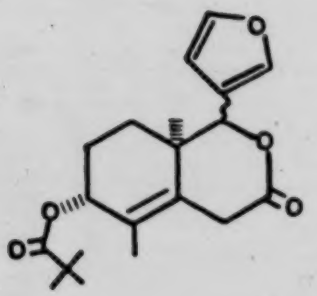


124

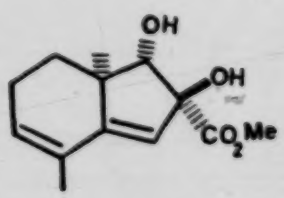


124a

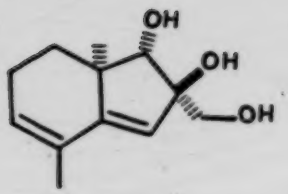


125

The first solution that comes immediately to mind in order to suppress undesirable side reactions is to reduce the number of such electrophilic centers. On the basis of this premise, the heteroannular diene portion of **63** was introduced by exposure of diol **117** to p-toluenesulfonic acid in refluxing acetone for 3 hr. The sole product of this reaction, formed in 69% yield, was determined to possess structure **126** by ^{1}H nmr spectroscopy. Accordingly, two vinylic protons were observed at δ5.66 (broad) and 5.29 (singlet). To our dismay, diene **126** yielded a plethora of unidentified products when treated with lithium hydroxide in aqueous methanol, presumably as a result of a competitive retroaldol process which would furnish a very delocalized enolate ion. Moreover, treatment of **126** with an excess of lithium aluminum hydride in the expectation of obtaining triol **127**, an immediate precursor of **63**, also gave a myriad of unrecognizable products.



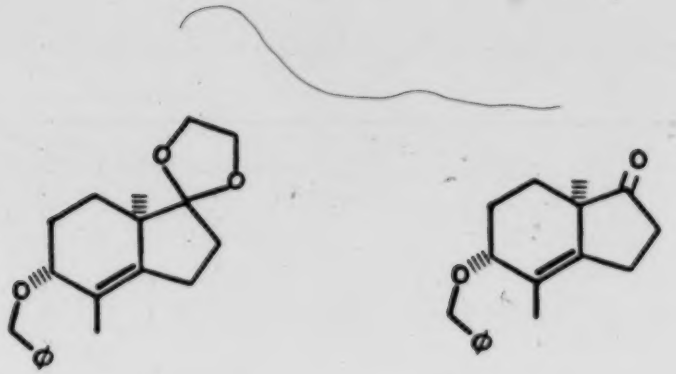
126



127

The most notorious drawback of the previous scheme is the lack of efficiency in various steps, especially on large scale experiments. In particular, a number of selective hydrolyses need to be performed in order to adequately functionalize the five-membered ring, a protocol that inevitably augments the number of synthetic operations. Therefore, improvements in the sequence were deemed highly desirable. Reasoning that one of the decisive factors causing the low overall yields was the presence of the pivalate group, our next task was to substitute it by a protecting group more resistant to alkaline conditions. Of the several alternatives available, a benzyloxy group seemed the most attractive since it can be introduced in basic media and may be removed, if necessary, under neutral conditions.

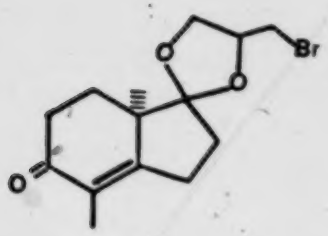
The reaction of **99** with benzyl bromide in the presence of sodium hydride and sodium iodide in DME gave the expected benzyl ether **128** in 48% yield. Considerably better efficiency was achieved (61%) when the solvent was replaced by HMPA. Further improvement was realized when potassium hydride in DME was used. This combination afforded **128** in 82% yield. Compound **128** showed the aromatic protons at δ7.32 as a multiplet and the benzylic protons as an AB system, J = 12 Hz, at δ4.62 and 4.46 in the ^{1}H nmr spectrum. Not totally unexpectedly, serious obstacles were encountered during the deketalization of **128**. Silica gel in wet CH_2Cl_2/Me_2CO[57] and boric acid in aqueous acetone[57] left **128** intact. Periodic acid in aqueous acetone[57] gave in turn a complex mixture of products. The conditions (aqueous hydrochloric acid, -12° → 20°C, 45 min) used to deblock successfully compound **100**, gave ketone **129** in only 48% yield (optimized!), with a number of by-products accounting for the rest of the mass balance. Aqueous fluoboric acid behaved analogously to hydrochloric acid.



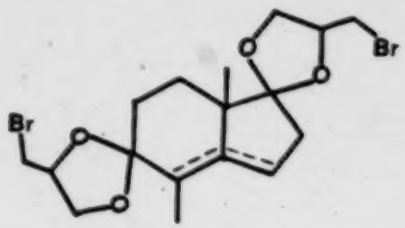
128 129

An appealing alternative to surmount the above difficulties would be to replace the ketal protecting group by another functionality that could perhaps be removed under neutral conditions. In this regard, Corey has reported[58] on the advantages of using bromomethyl ethylene ketals to protect acid-sensitive aldehydes and ketones, since it can be removed under mild conditions using zinc in methanol. In our present case, the reaction of diketone **95** with 3-bromo-1,2-propanediol[59] in the presence of p-toluenesulfonic acid in refluxing benzene afforded an equimolar mixture of ketals **130** and **131** as mixtures of epimers. This was of no consequence, as upon treatment of the crude mixture with p-toluenesulfonic acid in acetone at room temperature, selective cleavage of the

allylic ketal was observed and 130 was isolated in 74% yield after chromatography. A small amount (5-8%) of the unconjugated diketal 132 could be removed during the purification process.



130



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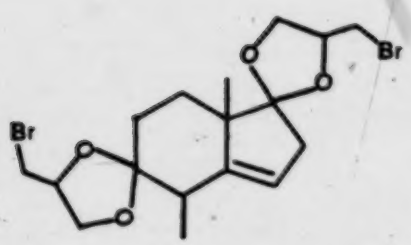
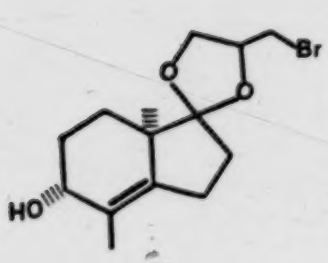


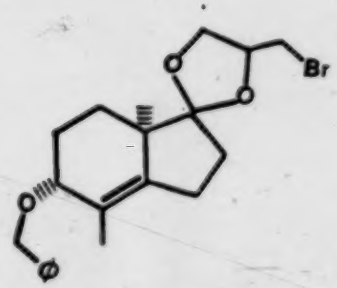
132

The reduction of 130 to the allylic alcohol 133 proceeded uneventfully in 83% yield using sodium

borohydride in methanol. Here too, only the cis isomer was obtained. Alternatively, diketone 95 could be converted to 133 in 84% overall yield when the intermediate purifications were omitted. Williamson reaction of 133 with benzyl bromide gave 134 as described for 99. In view of the chemical instability of 134 toward chromatographic purification, the crude product was used as such for the next step.



133



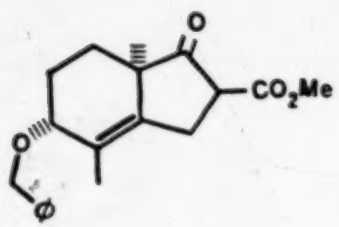
134

Quite unexpectedly, reductive deketalization of 134 using zinc in methanol[58] afforded ketone 129 in 39% yield at best. The use of acetic acid as the solvent instead of

methanol or variation of the temperature had little effect. However, acid hydrolysis of **134** using hydrochloric acid in aquecus acetone (-70° → 0°C, 3 hr) afforded cleanly ketone **129**. If the Williamson reaction and the hydrolysis of the ketal are effected with no intermediate purifications, compound **129** can be routinely produced in 72% overall yield from **133**.

Further conversion of **129** to diester **136** and alcohol **137** was effected as described for **101**. To this end, reaction of **129** with dimethyl carbonate and sodium hydride in THF or DME gave β-keto ester **135** in 65% yield as a colorless oil (ms 318.1673, $C_{20}H_{24}O_4$). Oxidation of the sodium enolate of **135** in THF or DME with benzoyl peroxide (-20° → room temperature) furnished diester **136** in 76% yield as a single isomer. As anticipated, compound **136** displayed the carbomethoxy carbonyl at δ168.02, the benzoate carbonyl at δ164.97 and the ketone carbonyl at δ209.18 in the ^{13}C nmr spectrum. Its mass spectrum showed the molecular ion peak at 448.1879, entirely consistent with the formula $C_{27}H_{28}O_6$. The reduction of **136** to alcohol **137** proceeded uneventfully in 100% yield using sodium borohydride in methanol. In analogy with compound **116**, a single epimer was also obtained. This was verified again by ^{13}C and ^{1}H nmr spectroscopy, which displayed a

unique set of signals. In the particular case of the former, the two expected carbonyl signals at δ170.55 (CO_2CH_3) and δ166.56 (benzoate) were observed. In addition, its ir spectrum showed two carbonyl bands at 1745 and 1719 cm^{-1} assigned likewise to the carbomethoxy and benzoate groups, respectively.



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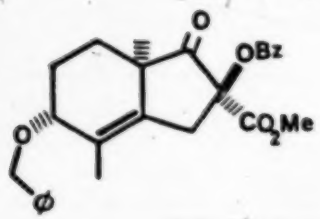

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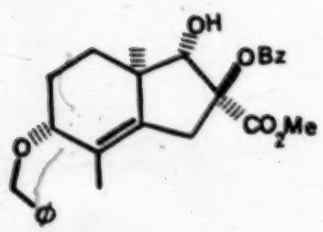
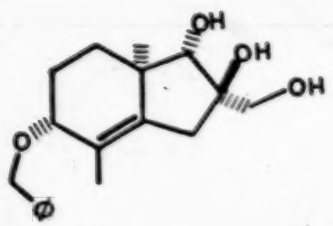
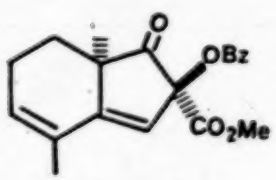


137

Attempted reduction of either 136 or 137 with lithium aluminum hydride yielded none of the expected triol 138. Only a multitude of unidentified products were obtained. Diisobutylaluminum hydride gave identical results, whereas lithium borohydride reduced 136 to 137 only. Similar observations pertain to the reduction of the inseparable 3.5:1 mixture of dienes 139 and 140, prepared by elimination of benzyl alcohol from 136 with p-toluenesulfonic acid in refluxing acetone.



138



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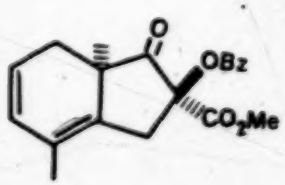

140

In spite of all these drawbacks, compound **137** engaged in rapid reaction with an excess of sodium methoxide in methanol to afford diol acid **141** in 64% yield, which in terms of efficiency represented a considerable improvement over the previous scheme.* Diol acid **141** represents an unparalleled probe to establish the relative stereochemistry between C-3 and C-9, and C-7 and C-8 by nmr techniques due to the chemical shift dispersion of its ^{1}H (400 MHz) and ^{13}C (100.6 MHz) nmr spectra. In the proton spectrum one observes the allylic methine proton as a doublet of doublets (J_1 = 7.5 Hz, J_2 = 7.5 Hz), due to coupling with the adjacent diastereotopic methylene protons. According to molecular models, the allylic hydrogen H_1 in the preferred conformation **142** of the <u>cis</u> isomer, where <u>cis</u> refers to the relative orientation of the benzyloxy group and the angular methyl group, displays a torsional angle of <u>ca.</u> 120° with respect to H_2 and of approximately 20° with respect to H_3. In the <u>trans</u> isomer **143**, the torsional angle between H_1 and H_3 is close to 90°

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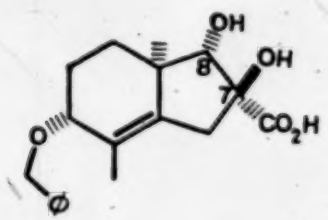
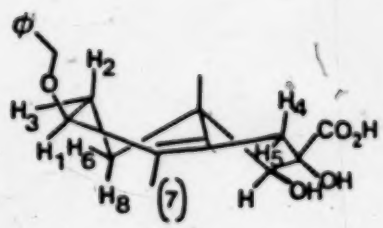
*Commercial sodium methoxide was used. The serendipitous presence of sodium hydroxide in this material undoubtedly caused the hydrolysis of the methyl ester. Interestingly, no benzoic acid could be detected in the crude mixture. Only methyl benzoate was produced.

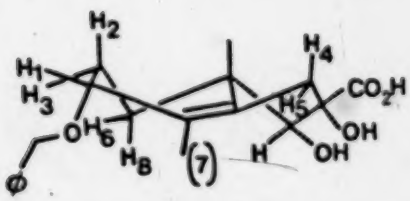
whereas that between H_1 and H_2 is about 15°. On this premise, one would expect a very different coupling pattern for H_1 in **143**. It should be pointed out that the presence of the double bond in the six-membered ring limits the flexibility of the molecule so that the angles indicated above are not expected to fluctuate to a large extent.



141



142



143

To support these assumptions, a computer simulation of the ^1H nmr spectrum of **141** was undertaken and the results are shown in Figure 1 and Figure 2. A long range coupling of 2.8 Hz between H_1 and H_4 (or H_5) was resolved in the Gaussian transformed spectrum and this value was included in the computations, as well as long range couplings between H_1 and H_5, H_6, H_7 and H_8. The linewidth assumed was 2.45 Hz. As can be seen in Figure 1, a very good correlation exists between the experimental and calculated spectra for the cis isomer. The small differences are due to the difficulty of determining precisely the values of all long range couplings. Figure 2 compares the experimental spectrum of **141** and the calculated spectrum for the trans isomer **143**. Nearly all the parameters have been kept constant, except that $J_{1,3}$ and $J_{1,2}$ were assumed to be 0 Hz and 8.3 Hz, respectively, to take into consideration the different torsional angles. In addition, $J_{1,6}$ was incremented from 1.1 Hz to 2.6 Hz to take into account the W-arrangement between these two protons. Needless to say, the agreement is very poor. In addition to this, Corey has very recently presented conclusive chemical evidence to validate the above nmr arguments.[60] The unambiguous assignment of the C-7 and C-8 stereochemistry relied more heavily on ^{13}C nmr

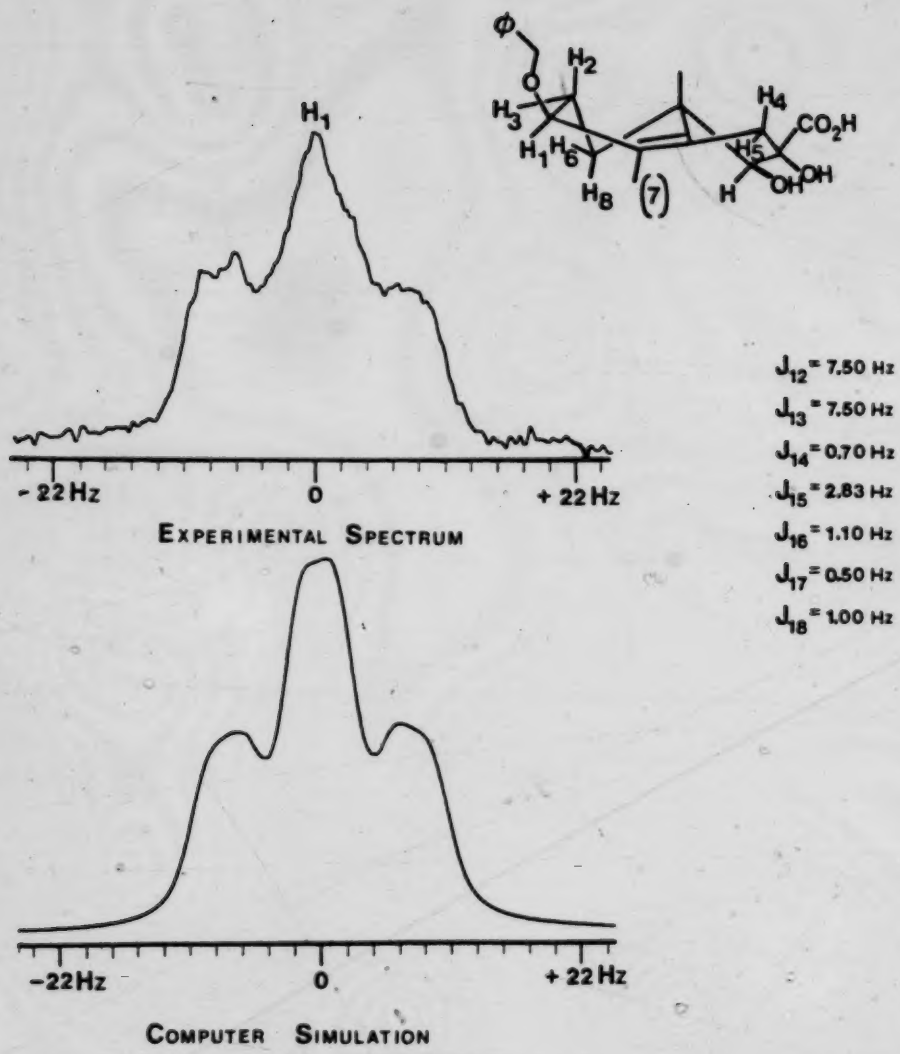


Figure 1. Computer simulation of the nmr spectrum of the allylic methine proton of the cis isomer **141**.

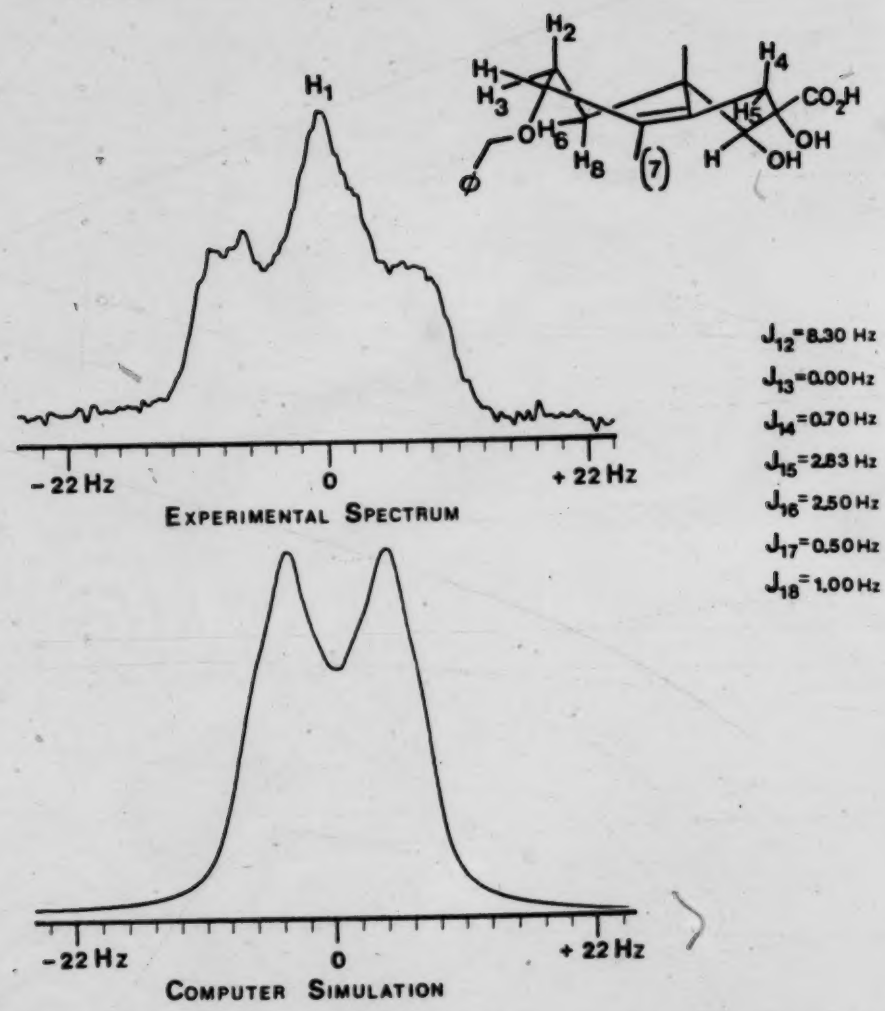
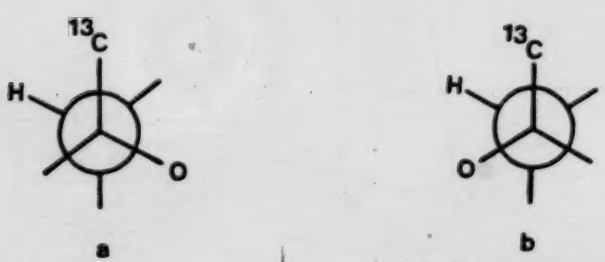


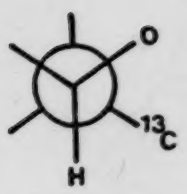
Figure 2. Computer simulation of the nmr spectrum of the allylic methine proton of the trans isomer **143**.

data. From the standpoint of stereochemical effects, spin-spin interactions between ^{13}C and ^{1}H nuclei separated by three bonds show much of the character of ^{1}H-^{1}H coupling. However, a number of factors other than dihedral angle can contribute to the absolute value of $^{3}J_{C-H}$. These include variables as the orientation of electronegative atoms appended to the interaction pathway. Hence, an antiperiplanar oxygen as in a is associated with a gauche ^{13}C-^{1}H coupling of <1 Hz, whereas in b the coupling is 2-3 Hz.[61]



Moreover, from the carbohydrate field it has been known for some time that an oxygen atom antiperiplanar to a ^{13}C nucleus in a gauche ^{13}C-^{1}H interaction decreases the absolute value of $^{3}J_{C-H}$ (<1 Hz) whereas a synclinal oxygen

with respect to a ^{13}C nucleus in a gauche ^{13}C-^{1}H coupling connectivity leads to somewhat increased values of $^{3}J_{C-H}$ (2-3 Hz).[61]



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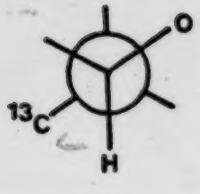
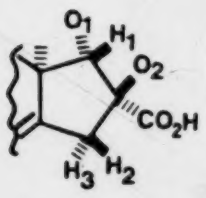


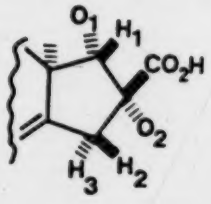
d

Close examination of the five-membered ring of **144** shows that the arrangement displayed between the carbonyl carbon, O_2 and H_3 is similar to the Newman projection a, whereas the coupling connectivities $CO-O_2-H_2$ and $CO-O_2-H_1$ resemble the projection b. Thus the multiplicity of the carbonyl carbon was expected to display two large $^{3}J_{C-H}$ couplings and one small (perhaps zero) coupling to H_3. Also, the coupling line $CO-O_1-H_1$ is analogous to the Newman projection c but not d. This would simply tend to increase the absolute value of $^{3}J_{C-H_1}$. Following similar lines, one would expect for the hypothetical isomer **145**

only one large $^{3}J_{C-H_3}$ and two small (possibly zero) $^{3}J_{C-H_1}$ and $^{3}J_{C-H_2}$ couplings. In the experimental ^{13}C nmr spectrum of **141** recorded at 100.6 MHz under proton gated decoupling conditions, the carbonyl carbon appeared as a doublet of doublets, J_1 = 4.03 Hz and J_2 = 4.03 Hz. Exponential weighing failed to reveal the presence of any other couplings. Thus, on the basis of the above arguments, the correct configurations of C-7 and C-8 are as shown in **141** and not as in **143**. Moreover, this fully agrees with the observation made previously that attempted oxidation of **117** with sodium periodate resulted in the complete recovery of the starting material.



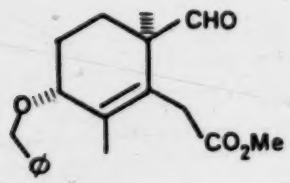
144



145

What was needed at this point was only to break the five-membered ring or to convert **141** to triol **138** before

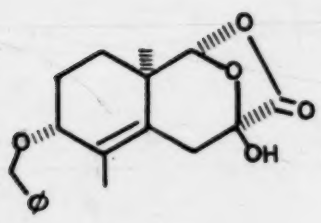
cleavage. In order to circumvent the low yields realized during the reduction of the carboxylic acid group of **118** with borane-methyl sulfide, compound **141** was exposed to an excess of lithium aluminum hydride in ether at 0°C. The desired triol **138** was indeed isolated, although in disappointingly low yields. Attempted *in situ* oxidation of the resulting triol with periodic acid in aqueous methanol failed to yield perceptible amounts of aldehyde **146**.



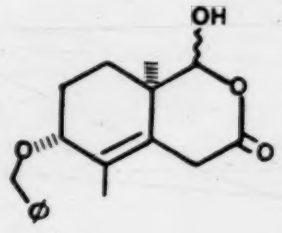
146

Attention was then turned to direct oxidation of **141**. As anticipated, treatment of **141** with periodic acid in acetone gave very cleanly (99%) the tricycle **147**. In analogy with **119**, compound **147** also displayed an infrared absorption band at 1802 cm^{-1} ascribed to the acetal

lactone moiety. It may be easily recognized that **147** possesses a masked α-keto acid moiety and should, at least in principle, be susceptible to further oxidation to lactol **148**. In practice however, **147** was recovered unchanged or completely destroyed after prolonged treatment with hydrogen peroxide in methanol or with periodic acid in refluxing butanone, respectively.



147



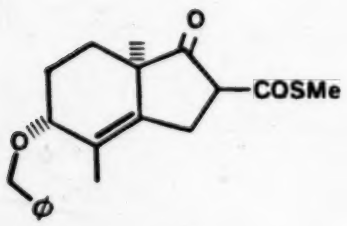
148

It was precisely at this time that a related scheme, although more efficient in terms of overall operations, was devised. The most salient feature of this modification pertained to the substitution of the methyl ester of **136** by a thioester, a reasonably stable functional group showing a remarkable proclivity to

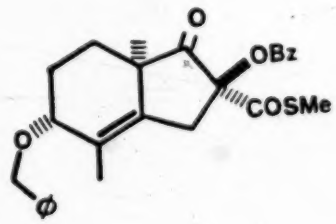
undergo reduction by sodium borohydride.[62] In other words, the expectations were that the simple replacement of the CO_2Me group by a COSMe moiety would permit the simultaneous reduction of the ketone and the thioester portions of **136** to give directly a primary and a secondary diol. Along this line of reasoning, ketone **129** was treated with S,S'-dimethyl dithiocarbonate.[62] Using the reported conditions (sodium hydride in DME), the conversion of **129** to the expected β-keto thioester **149** proceeded in very low yield, with a large number of by-products being detected on TLC. The use of dimethylformamide as solvent led to a modest improvement in yield (40%). Considerably better yields were realized by the use of potassium hydride in HMPA. Under these conditions, the thioacylation reaction proceeded rapidly (and sometimes violently) at ambient temperature. Nevertheless, compound **149** was found by ^1H nmr spectroscopy to contain variable (20-40%) amounts of an unidentified impurity which could not be separated chromatographically.

By considerable experimentation, it was discovered that the best conditions for the oxidation of **149** to **150** with benzoyl peroxide necessitated the utilization of potassium hydride as the base. In this regard, sodium

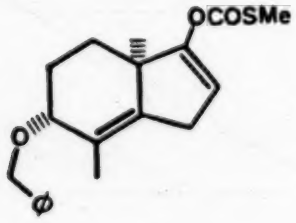
hydride proved to be quite inefficient. Moreover, if the oxidation step is carried out with the unpurified β-keto thioester, reproducible yields of 51% from **129** could be realized. Variable amounts (ca. 20-40%) of the starting ketone **129** were found to contaminate the oxidation product **150**. The separation of **129** from **150** could not be effected by chromatographic means. Thus, it appears that O-acylation of the potassium enolate of **129** to give **150** effectively competes with the formation of **149**. Conclusive evidence of the presence of **150** is however, not yet available. As it appears, the new functional group had no effect on the stereochemical outcome of the oxidation with benzoyl peroxide, as a single diastereomer was also obtained in this case. This aspect was corroborated by subsequent transformations.



149



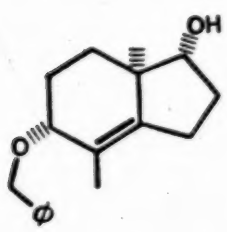
150



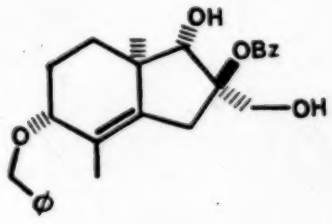
151

With compound **150** in hand, its reduction with sodium borohydride was explored. Treatment of an ethanol solution of **150** at 0°C with a large excess of sodium borohydride led to the rapid consumption of the starting material. However, four major different products were discernible on TLC. The least polar was identified as alcohol **152** by spectroscopic means. The methine proton of the secondary alcohol appeared as a doublet of doublets, J_1 = 10 Hz and J_2 = 8 Hz at δ3.59 in the ^{1}H nmr spectrum. In addition, the presence of the hydroxyl group was evident in the infrared spectrum which showed a broad band at 3400 cm^{-1}. Further structural confirmation derived from the conversion of **152** to **129** in 30% yield by oxidation with pyridinium chlorochromate in methylene chloride.[27] Alcohol **152** was formed by simple reduction of **129** present along with **150** in the reaction mixture. The other three components could not be cleanly separated chromatographically, but were readily characterized by 400 MHz ^{1}H nmr spectroscopy as a mixture of three possible diol benzoates **153**, **154**, and **155**, produced by migration of the benzoyl group of **153** over the two free hydroxyl groups. The combined yield of **153**, **154** and **155** was 53% on the basis of the amount of **150** present at the onset. Further confirmation of the isomeric nature of **153**, **154**

and **155** was obtained from their conversion to a single triol **138**, identical by nmr analysis with the material prepared by reduction of **141**, by treatment with lithium hydroxide in aqueous methanol. Crystalline **138**, obtained in 93% yield, displayed three ^{13}C signals at δ81.26 (singlet), 79.77 (doublet) and 71.27 (triplet) in the ^{13}C nmr spectrum, and were assigned to the tertiary, secondary and primary alcohols, respectively.



152



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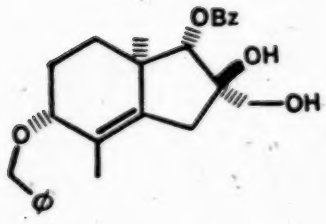

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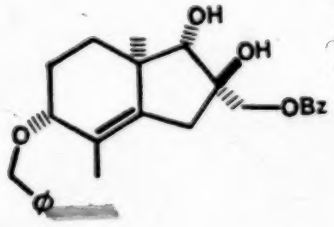
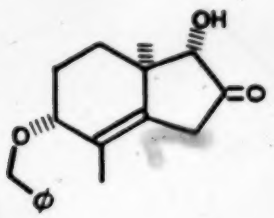


155

Having achieved the proper functionalization of the five-membered ring in a reasonably short manner, it became necessary to convert it to the hexanolide portion of **63**. To this end, exposure of **138** to lead tetraacetate in aqueous acetic acid afforded the expected lactol **148**. Nevertheless, the yields were found to vary dramatically with the amount of triol employed. When **138** was treated with sodium periodate in aqueous acetone, one major product, characterized as ketol **156** by spectroscopic methods, was isolated in 67% yield. Compound **156** was quite reluctant to undergo further oxidation of the acyloin moiety, and the use of more forcing conditions such as increasing the temperature, led to considerable destruction of the molecule. It was very pleasant to find that the use of periodic acid, a stronger oxidant than sodium periodate, afforded **148** as a 5:1 mixture of epimers in a satisfactory 60% yield. The presence of approximately 50% of the corresponding open monocyclic aldo acid was also established by ^1H nmr spectroscopy. Compound **148** showed a molecular ion at 302.1526 in the high resolution mass spectrum, which was consistent with the molecular formula $C_{18}H_{22}O_4$. Also, its ir spectrum portrayed the lactol moiety at 3360 cm^{-1} (OH) and 1729 cm^{-1} (carbonyl). It may now be readily seen that what is

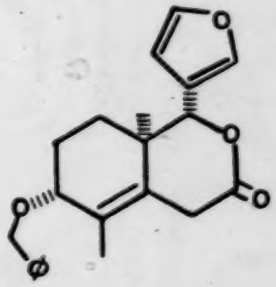
needed to complete the synthesis of **63** is the incorporation of the β-furan ring into **148** and the elimination of benzyl alcohol to install the second double bond.



156

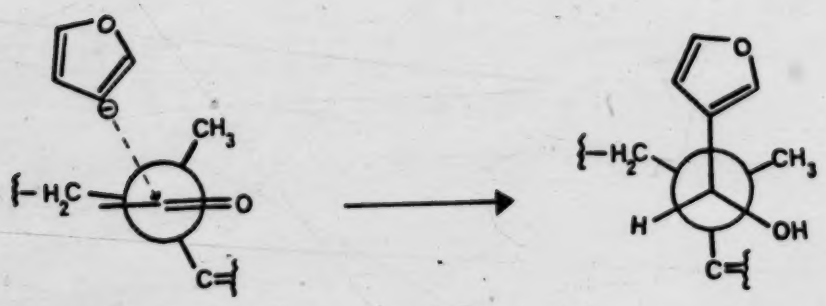
Several difficulties were encountered when attempting to engage the latent aldehyde group of **148** into reaction with β-lithiofuran. The initial experiments were very disappointing. Eventually it was discovered that an excess (ca. 10 equivalents) of the organometallic reagent at room temperature gave the best results providing compound **157** in 43% yield. Unexpectedly, only one isomer was produced according to ^{13}C nmr analysis (100.6 MHz), which showed a single set of signals, including two α-furan carbons at δ142.97 and 141.05 as well as a β-furan

carbon at δ109.91. In its 200 MHz ^{1}H nmr spectrum, the β-furan proton was observed at δ6.41 as a doublet of doublets, J_1 = 2 Hz and J_2 = 1 Hz, whereas the two α-furan protons appeared at δ7.45 (dd) and 7.42 (dd). The presence of the furan ring was also unequivocally confirmed in the FTIR spectrum which displayed a small band at 3135 cm^{-1}. The stereochemistry shown in **157** rests on two pieces of evidence. Firstly, by saturation of the angular methyl group, a +5.7% enhancement in the integral of the furan β-proton and a +0.7% in the intensity of the proton adjacent to the furan ring were observed in the difference Overhauser experiment. And secondly, compound **157** could be transformed into **63** by elimination of the elements of benzyl alcohol.



157

Mechanistically, the reaction follows strictly the Anh model of nucleophilic additions to carbonyl compounds.[63] This point is better illustrated by making reference to the Newman projections below. If one assumes that of all the three substituents on the carbon supporting the aldehyde group, the methyl is the smallest, the methylene the medium and the vinylic carbon the largest, then it is an easy matter to realize that the β-furyl anion (or radical) will approach the carbonyl carbon between the smallest and medium substituents with an angle of incidence of 100-107° due to pyramidalization of the carbonyl LUMO in the transition state, and antiperiplanar with respect to the largest group. This leads precisely to the observed relative stereochemistry (**9R***, **10R***).

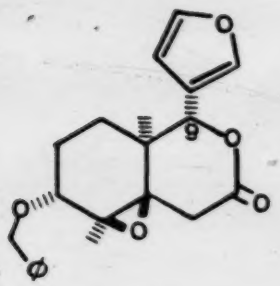


Exposure of **157** to a number of bases such as 1,5-diazabicyclo[5.4.0]undec-5-ene in benzene, lithium diisopropylamide in THF or potassium hydride in DME led to destruction of the starting material. However, brief exposure to a freshly prepared solution of potassium t-butoxide in DME led to an immediate elimination of benzyl alcohol and to the formation of lactone **63** in 82% yield after flash chromatography. Compound **63** prepared in this way displayed a ^{1}H nmr spectrum (400 MHz) in agreement with the reported data.

For further synthetic manipulations directed toward the elaboration of **15**, it appeared most appealing to utilize compound **157** since it already possesses a potential leaving group at C-3. With this idea in mind, compound **157** was treated at room temperature with m-chloroperbenzoic acid in chloroform to form the tetrasubstituted epoxide ring. According to kinetic ^{1}H nmr analysis, competitive oxidation of the unsubstituted double bond of the furan ring was taking place under these conditions. This side reaction could be minimized by stopping the reaction after two hours and resubjecting the recovered starting material, which is chromatographically inseparable from the epoxide, to the treatment with

MCPBA. The yield of epoxide **158** could be improved to 50% after two repetitions of the sequence. This material however, contained ca. 10-15% of **157** as shown by ^1H nmr integration. This did not impede **158** from being characterized by the common spectral means. In particular, high resolution mass spectrometry revealed a molecular weight of 272.1393 ($C_{17}H_{20}O_3$) which corresponds to the expected molecular formula ($C_{22}H_{24}O_4$) less β-furfural. It is worth mentioning that compound **158** was stereochemically homogeneous. Its configuration at C-4 and C-5 could be readily elucidated by the large (0.4 ppm) downfield shift experienced by the proton adjacent to the furan ring when compared to **157**. Therefore, the epoxide oxygen must be on the same side as the proton on C-9. Epoxide **158** underwent a very facile ring opening reaction in the presence of potassium t-butoxide in DME at 0°C, giving alcohol **159** in 65% yield after chromatography. A new vinylic proton was observed at δ6.49 as a sharp singlet in the spectrum of **159**, assigned to the proton adjacent to the lactone carbonyl. Finally, exposure of a pyridine solution of **159** to thionyl chloride at 0°C provided two principal products, identified as dienes **160** and **161** in 30% and 16% yield (unoptimized), respectively. In an attempt to improve the yield of this

last transformation, it was found that the use of collidine instead of pyridine gave preponderantly the undesired isomer **161**.



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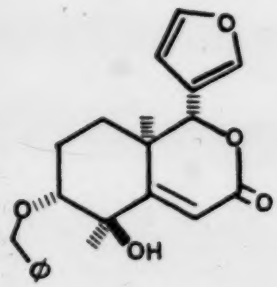

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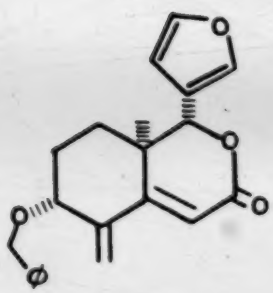

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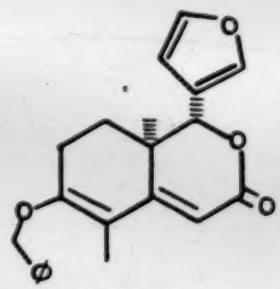
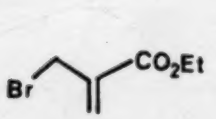


161

With the synthesis of the CD synthon complete, it was considered appropriate to investigate its coupling with **14**. In a series of model experiments, **14** proved to be an

excellent nucleophile in Michael additions to bromo ester **162**,[64] reacting exothermically in the presence of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) to provide diketo ester **163** in 56% yield. However, the attempted coupling of optically active **14** with racemic **160** using DBU as base led to the complete recovery of both starting materials, even under forcing conditions. Other basic catalysts such as potassium t-butoxide in DME or cesium carbonate in N-methyl pyrrolidone at 85°C proved equally ineffective. Similar results were also obtained in the attempted coupling via the π-allyl palladium complex **164**.[65] In no single case were we able to detect the formation of seco acid **13** or its diastereomer **16**.



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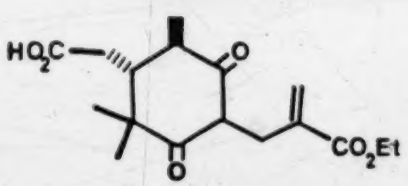

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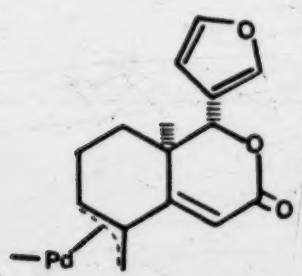
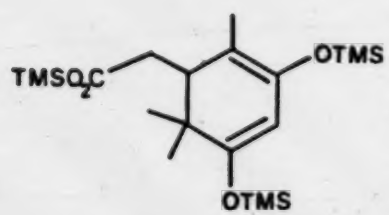


164

The Michael addition of **14** to **160** under acidic conditions was also briefly examined. Treatment of racemic **14** with a five-fold excess of trimethylsilyl trifluoromethanesulfonate in triethylamine for 90 min afforded diene ester **165** in 74% yield. In analogy with the above results, no reaction was observed when a solution of **160** and an excess of **165** was exposed to titanium tetrachloride under the conditions developed by Mukaiyama.[23]



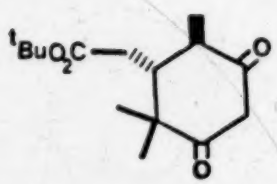
165

Since in mexicanolide the acetic acid chain appended to the A ring occurs as the methyl ester, several attempts

were made to selectively esterify **14** without disturbing the β-diketone system. Very disappointingly, no discrimination was observed when **14** was exposed in succession to phenyldichlorophosphate and methanol,[36] to diazomethane, to methanesulfonyl chloride and methanol, or to carbonyldiimidazole and methanol. However, as a test for the coupling reaction, the corresponding t-butyl ester **166** was prepared in the following manner. Exposure of optically active keto acid **29** in succession to oxalyl chloride in benzene containing a trace of dimethylformamide and then to t-butanol in pyridine-dimethylaminopyridine afforded diester **167**, $[\alpha]_D$ = -5.6° (CH_2Cl_2), in 54% yield over the two steps. The presence of a singlet at δ1.45 integrating for nine protons in the ^1H nmr spectrum, as well as a singlet at δ27.96 in the ^{13}C spectrum supports the structure. When a solution of **167** in DME was treated with lithium t-butoxide at reflux, a single β-diketone **166**, $[\alpha]_D$ = -11.3° (CH_2Cl_2), was produced in 87% yield. Interestingly, compound **166** exists in solution ($CDCl_3$) almost exclusively in the β-diketone form. This was clearly appreciated in the ^1H nmr spectrum, which showed the methylene protons adjacent to the two carbonyls as an AB system, J = 17 Hz, at δ3.53 and 3.47. Contrary to the expectations, the reaction of the

potassium enolate of **166** with **160** resulted in the quantitative recovery of both starting materials. The addition of 18-crown-6 to the reaction mixture had no effect on the formation of seco acids **13** or **16**.

The notorious proclivity of diketo acid **14** to react with bromo ester **162** suggested that a possible means to overcome our incapacity to unite the A ring with the CD fragment could be the further manipulation of **160** to the allylic bromides **168** or **169**. It is expected that the presence of a better leaving group in **168** or **169** can surmount the energy barrier for an efficient A-CD coupling. This idea is currently being investigated.



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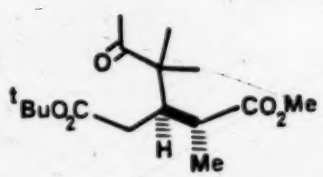

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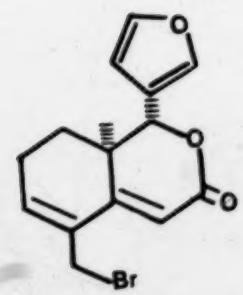

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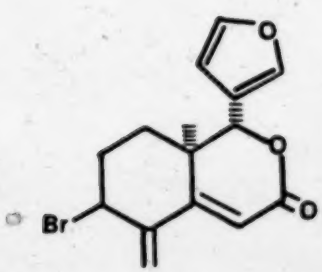

169

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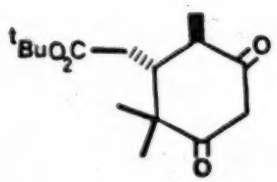

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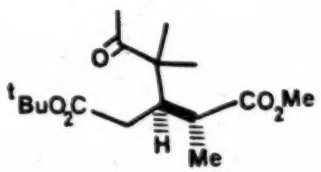

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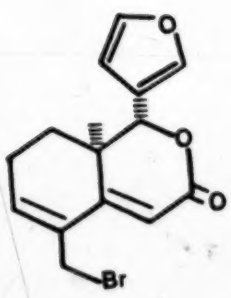

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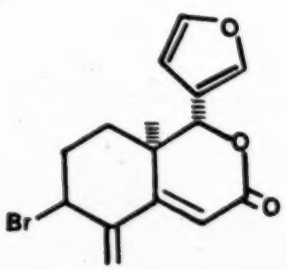

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EXPERIMENTAL

1. General

Melting points were recorded on a Köfler hot stage apparatus or a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra (ir) were determined using the following spectrophotometers: Perkin-Elmer model 457, model 297, Nicolet 7199 FTIR and Nicolet MX-1 FTIR. Mass spectra (ms) were obtained using an AEI MS50 high resolution mass spectrometer and low resolution spectra on an AEI MS12 spectrometer. Gas chromatographic analyses were performed on a Hewlett-Packard 5750 instrument using a column of 15% SE-30 on Chromosorb W with helium as the carrier gas. Elemental analyses were performed by the microanalytical laboratory of this department. Samples were routinely dried at 40-60°C/1 torr prior to analysis. High pressure liquid chromatography (HPLC) was carried out using a Waters prep500 LC system with a refractive index detector. Proton nuclear magnetic resonance spectra (^{1}H nmr) were obtained using the following spectrometers: Varian EM-360 (60 MHz), Varian A-56/60 (60 MHz), Bruker WP-80 (80 MHz), Varian HA-

100/Digilab-12 (100 MHz, interfaced to a Nova 1200 computer), Bruker WH-200 (200 MHz) and Bruker WH-400 (400 MHz). Fluorine nuclear magnetic resonance spectra (^{19}F nmr) were recorded at 376 MHz on a Bruker WH-400 spectrometer using C_6F_6 as the internal standard. Carbon-13 nuclear magnetic resonance spectra (^{13}C nmr) were recorded on a Bruker WP-60/NIC-80 (15 MHz), Bruker WH-200 (50.3 MHz) and Bruker WH-400 (100.6 MHz) spectrometers. Carbon-13 multiplicities were derived from off-resonance or Carr-Purcel-Meiboom-Gill spin echo J-modulated experiments.[17] Proton spin-lattice relaxation times (T_1) were measured at 200 MHz using the t-180°$_x$-t-90°$_x$-acquisition inversion-recovery pulse train. A memory size of 4K data points was invariably used. Nuclear Overhauser Enhancement (NOE) experiments were determined in the difference mode in which a control (undecoupled) spectrum was computer-subtracted from the irradiated spectrum after Fourier transformation. Alternatively, all the data points of the control spectrum were made negative and computer-added to the FID of the decoupled spectrum before Fourier transformation. Positive enhancements are defined as multiplets possessing an antiphase with respect to the decoupled signal. Nmr spectral simulations were performed on a 24 bit word-length Aspect 2000 computer with 80K RAM

using the standard Bruker PANIC program. Samples for T_1 and NOE measurements were deoxygenated with helium gas for 10-15 min prior to use. Two dimensional (2D) Nuclear Overhauser Enhancement nmr experiments (NOESY) were performed using the Bruker software package.[51] Normally 16 scans per FID were accumulated to fulfill the 16-transient phase program, which provided quadrature detection in F_1. Generally, 1K × 128 or 1K × 256 data points were stored on disk and were zero-filled to 256 and 512 points in F_1, respectively, during Fourier transformation. Sine bell digital filtering applied in both dimensions gave the best resolved spectra although a Gaussian transform in F_1 and a Lorentz transform in F_2 were occasionally employed. A Bruker satellite station equipped with a high speed color graphics televideo scanner was used for transforming and plotting 2D data matrices. ^1H multiplicities were occasionally derived from resolution-enhanced spectra. Separations by spinning band distillation were carried out in Perkin-Elmer NFT-51 annular still. A Perkin-Elmer 241 polarimeter was used for measuring all optical rotations. Circular Dichroism (CD) spectra were recorded on a Jasco ORD/UV-5-SS-20-20 instrument. Ultraviolet (uv) spectra were recorded on an Unicam 1700 spectrophotometer. Ozone was generated using a Welsbach ozonator (80 V).

2. Materials

Flash chromatography was performed according to the procedure of Still[66] using silica gel of 230-400 mesh and thin layer chromatography using Merck Kieselgel 60 GF_{254}. Solvents were purified as follows: tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) by distillation from a blue or purple solution of sodium benzophenone ketyl under an argon atmosphere; dimethylsulfoxide (DMSO), dimethylformamide (DMF), hexamethylphosphoramide (HMPA) and collidine by distillation over calcium hydride at reduced pressure triethylamine, tetramethylethylenediamine (TMEDA) and pyridine by distillation over calcium hydride; ethyl ether by distillation over lithium aluminum hydride; methanol by distillation over magnesium methoxide and methylene chloride over phosphorus pentoxide. All solvents were stored over 3 Å molecular sieves after distillation.

(+) Campholenic acid (18)

Potassium hydroxide (120 g of 85% material, 1.82 mol) was melted in a porcelain casserole using a Merck burner. d-Camphorsulfonic acid (17) (88.16 g, 0.35 mol) was added in portions over a 15 min period with continuous stirring. After the addition was complete, the dark

mixture was heated for an additional 15 min and then cooled down to ambient temperature. The brown solid was dissolved in 900 ml of water and filtered to remove some polymeric material. The filtrate was then extracted two times with ether. The ether extracts were discarded. To the aqueous solution was added carefully aqueous HCl until pH 1. (Caution: SO_2 is liberated in this step.) The solution was then extracted with methylene chloride. The organic extracts were dried (Na_2SO_4), filtered and concentrated to leave a brown viscous residue which was purified by short path distillation to furnish (+)-campholenic acid **18** (32.4 g, 51%) as a colorless viscous oil: b.p. 95-97°C/0.6 torr. $[\alpha]_D^{23}$ = +8.1° (c = 1.1, $CHCl_3$). ^1H nmr (400 MHz, $CDCl_3$) δ 5.23 (br.s, 1H, =CH-), 2.48 (dd, 1H, J = 16, J' = 4 Hz, $-CH_2CO_2-$), 2.43 (m, 1H, $-C\underline{H}_2CH=$), 2.28 (m, 2H), 1.93 (m, 1H, $-CH_2C\underline{H}CH_2-$), 1.61 (m, 3H, $=CCH_3$), 1.02 (s, 3H, $-CH_3$) and 0.81 (s, 3H, $-CH_3$). ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 180.51, 147.67, 121.57, 46.75, 46.13, 35.54, 35.19, 25.45, 19.69 and 12.41. ir (neat) 3500-2300 (CO_2H), 1715 (C=O) and 1370 cm^{-1} (gem CH_3). ms M^+ 168.1153 (calcd. for $C_{10}H_{16}O_2$: 168.1151). Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.38; H, 9.59. Found: C, 71.35; H, 9.70.

(+)-Methyl campholenate (19)

Dry potassium carbonate (60 g, 0.436 mol) was suspended in acetone (175 ml). A solution of (+)-campholenic acid (18) (73.3 g, 0.436 mol) in acetone (200 ml) was added from a dropping funnel and the suspension was stirred mechanically for 10 min. Methyl iodide (54.3 ml, 0.872 mol) was added and the reaction mixture was heated at reflux overnight. After cooling to room temperature, the suspension was filtered and the residue washed several times with acetone. The solvent was then evaporated *in vacuo* and the residue partitioned between aqueous sodium chloride and ether. The aqueous solution was further extracted with ether. Drying of the organic extracts (Na_2SO_4), filtration and concentration under reduced pressure gave a pale yellow liquid. Short path distillation under reduced pressure delivered (+)-methyl campholenate (19) (80 g, 100%) as a colorless liquid: b.p. 78°C/3 torr. $[\alpha]_D^{22}$ = +11.5° (c = 1.0, $CHCl_3$). ^1H nmr (400 MHz, $CDCl_3$) δ 5.22 (br.s, 1H, $-CH^-$), 3.68 (s, 3H, $-OCH_3$), 2.43 (d, 1H, J = 10 Hz, $-CH_2CO-$), 2.37 (m, 1H, $-CH_2CH=$), 2.24 (m, 2H), 1.89 (m, 1H, $-CH_2CHCH_2-$), 1.70 (m, 3H, $=CCH_3$), 1.00 (s, 3H, $-CH_3$) and 0.79 (s, 3H, $-CH_3$). ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 173.86, 147.88, 121.85, 51.23, 46.87, 46.60, 35.79, 35.23, 25.63, 19.82 and

12.57. ir (neat) 3050 (C=CH) and 1740 cm^{-1} (ester C-O). ms M^+ 182.1309 (calcd. for $C_{11}H_{18}O_2$: 182.1308). Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.47; H, 9.96. Found: C, 72.39; H, 10.05.

(-)-Methyl (2R,3R)-2,4,4,5-tetramethylcyclopent-5-enylacetate (28)

Diisopropylamine (0.26 ml, 1.88 mmol) was dissolved in THF (2 ml) under an atmosphere of argon at -76°C. A solution of methyllithium in ether (1.6 M, 1.02 ml, 1.65 mmol) was added dropwise via syringe and the solution was stirred for 20 min at that temperature. A solution of methyl campholenate (**19**) (200 mg, 1.1 mmol) in THF (2 ml) was also added slowly. After 50 min at -76°C, a solution of methyl iodide (0.206 ml, 3.3 mmol) in THF (2 ml) was injected. The cryogenic bath was removed and the mixture was allowed to warm to ambient temperature and stirred thereafter for 1 hr. 1N HCl was added and the product was extracted with ether. The extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to a yellow oil. Short path distillation afforded compound **28** (185 mg, 86%) as a colorless liquid: b.p. 79°C/3 torr. $[\alpha]_D^{23} = -34.8°$ (c = 1.005, CH_2Cl_2). ^1H nmr (400 MHz, $CDCl_3$) δ 5.22 (br.s, 1H, -CH=), 3.68 (s, 3H, $-OCH_3$), 2.55 (dq, 1H, J = 10.5, J' = 7

Hz, -CHCO-), 2.29 (m, 1H, -$C\underline{H}_2CH$=), 2.14 (db, 1H, J = 8, J' = 10.5 Hz, -$C\underline{H}_2CH$=), 1.89 (m, 1H, -$CH_2\underline{CH}CH_2$-), 1.58 (m, 3H, =CCH_3), 1.16 (d, 3H, J = 7 Hz, $\underline{CH}_3CH$-), 0.92 (s, 3H, -CH_3) and 0.86 (s, 3H, -CH_3). ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 176.56, 148.23, 120.35, 52.39, 50.51, 46.18, 40.08, 33.46, 25.11, 18.80, 16.73 and 11.97. ir (neat) 3050 (C=CH) and 1744 cm^{-1} (ester C=O). ms M^+ 196.1465 (calcd. for $C_{12}H_{20}O_2$: 196.1463). Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.41; H, 10.27. Found: C, 73.18; H, 10.33.

Methyl (2R,3R)-3-carboxymethyl-5-oxo-2,4,4-trimethyl-hexanoate (29)

A solution of ester **28** (2 g, 10.2 mmol) in methylene chloride (20 ml) and methanol (10 ml) was chilled to -78°C. A stream of ozone was passed through until a pale blue color persisted. At this point oxygen was bubbled through to drive-off excess ozone. A solution of triphenylphosphine (4.005 g, 15.3 mmol) in methylene chloride (20 ml) was then added slowly. When the addition was complete, the cryogenic bath was removed and the mixture permitted to come to room temperature and was stirred 8 hr thereafter. The solvents were evaporated in vacuo and the residual oil was dissolved in acetone (100

ml) and concentrated (aspirator). The residue was dissolved in acetone (200 ml) and cooled to 0°C. A 0.35 M solution of Jones reagent (48 ml, 16.8 mmol) was added rather rapidly. When the addition was complete, the reaction was allowed to proceed at room temperature for 1 hr. The solvent was evaporated under vacuum and the remaining dark oil was partitioned between ethyl acetate and aqueous sodium chloride. The organic solution was extracted with aqueous sodium bicarbonate. The aqueous layer was extracted once more with ethyl acetate and the organic extracts were discarded. Acidification of the aqueous solution with HCl to pH 1 was followed by extraction with ethyl acetate. Drying (Na_2SO_4), filtration and concentration gave ketoacid **29** (1.946 g, 78% overall) as a colorless oil, homogeneous on TLC: ^1H nmr (400 MHz, $CDCl_3$) δ 9.6-8.4 (br, 1H, $-CO_2H$), 3.66 (s, 3H, $-OCH_3$), 3.01 (dt, 1H, J = 8, J' = 4.5 Hz, $-CH_2\underline{CH}-$), 2.53 (dq, 1H, J = 4.5, J' = 7 Hz, -CHCO-), 2.43 (dd, 1H, J = 17, J' = 8 Hz, $-CH_2CO-$) 2.30 (dd, 1H, J = 17, J' = 4.5 Hz, $-CH_2CO-$), 2.24 (s, 3H, CH_3CO-), 1.15 (d, 3H, J = 7 Hz, $\underline{CH_3}-$) and 1.11 (s, 3H, $-CH_3$). ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 212.85, 178.16, 176.30, 51.83, 51.69, 41.26, 39.41, 31.83, 25.13, 22.33, 21.28 and 13.68. ir (neat) 3700-2200 (CO_2H) and 1720 cm^{-1} (C=O). ms m/e 227.1273 (M^+-17; calcd. for $C_{12}H_{19}O_4$: 227.1283).

(+)-Campholenol (**20**)

(+)-Methyl campholenate (**19**) (1.0 g, 5.5 mmol) was dissolved in ether (40 ml). Solid lithium aluminum hydride (209 mg, 5.5 mmol) was added in portions at room temperature under an argon atmosphere. Twenty minutes later, ethyl acetate was added cautiously to destroy excess reagent. When bubbling had subsided, aqueous sodium potassium tartrate was added and the product was extracted with ether. Drying (Na_2SO_4), filtration and concentration yielded a colorless liquid. Bulb-to-bulb distillation at reduced pressure gave (+)-campholenol (**20**) (760 mg, 90%) as a colorless viscous oil: b.p. 115°C (oven temp.)/4.5 torr. $[\alpha]_D^{23}$ = +4.3° (C = 0.987, CH_2Cl_2). ^1H nmr (400 MHz, $CDCl_3$) δ 5.24 (br.s, 1H, -CH=), 3.70 (ddd, 1H, J = 10, J' = 8.5, J" = 5 Hz, $-CH_2O-$), 3.62 (ddd, 1H, J = 10, J' = 8.5, J" = 6.5 Hz, $-CH_2O-$), 2.70 (s, 1H, -OH), 2.28 (m, 1H, $-\underline{CH_2}CH=$), 1.84 (m, 2H), 1.75 (m, 1H), 1.60 (m, 3H, $=CCH_3$), 1.54 (m, 1H), 0.97 (s, 3H, $-CH_3$) and 0.76 (s, 3H, $-CH_3$). ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 148.44, 121.49, 62.20, 46.64, 35.38, 33.11, 25.58, 19.61 and 12.47. FTIR ($CHCl_3$ cast) 3330 cm^{-1} (OH). ms M^+ 154.1357 (calcd. for $C_{10}H_{18}O$: 154.1358). Anal. Calcd. for $C_{10}H_{18}O$: C, 77.85; H, 11.77. Found: C, 77.69; H, 11.76.

(4R,5R)-3-Carboxymethyl-4,6,6-trimethylcyclohexane-1,5-dione (**14**)

Ketoacid **29** (1.946 g, 7.98 mmol) was dissolved in dry DME (30 ml). Solid lithium t-butoxide (2.552 g, 31.9 mmol) was added and the suspension was heated at reflux under an argon atmosphere for 2 hr. After cooling to ambient temperature, aqueous sodium carbonate was added and the solution was extracted twice with chloroform. The organic extracts were discarded. The aqueous solution was then acidified to pH 1 with HCl and extracted with ethyl acetate. The extracts were dried (Na_2SO_4), filtered and concentrated to yield a creamy-colored solid. Recrystallization from acetone-methanol gave β-diketone **14** (950 mg, 56%) as a microcrystalline white solid: m.p. (racemic) 207°C; m.p. (optically pure) 171.5-172°C. $[\alpha]_D^{22}$ = +57.8° (c = 1.0, MeOH). CD (MeOH) $\Delta\varepsilon_{277}$ = +2.97, $\Delta\varepsilon_{315}$ = -1.19. ^{1}H nmr (400 MHz, C_5D_5N) δ 5.77 (s, 1H, =CH-), 2.90 (dd, 1H, J = 17, J' = 3.5 Hz, $-CH_2CO-$), 2.80 (ddd, 1H, J = 12, J' = 6.5, J" = 3.5 Hz, $-CH_2\underline{C}H-$), 2.68 (dq, 1H, J = 12, J' = 7 Hz, $CH_3\underline{C}H-$), 2.63 (dd, 1H, J = 17, J' = 6.5 Hz, $-CH_2CO-$), 1.61 (d, 3H, J = 7 Hz, $\underline{C}H_3CH-$), 1.52 (s, 3H, $-CH_3$) and 1.24 (s, 3H, $-CH_3$). ^{13}C nmr (100.6 MHz, C_5D_5N) δ 175.92, 102.24, 46.06, 42.56, 40.31, 35.40,

23.50, 20.35 and 14.49. FTIR (MeOH cast) 3400-2000 (CO_2H and β-diketone), 1695 (acid C=O), 1623 and 1545 cm^{-1} (β-diketone). ms M^+ 212.1044 (calcd. for $C_{11}H_{16}O_4$: 212.1048). Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.23; H, 7.60. Found: C, 62.32; H, 7.71.

(3S,2'S)-4,4,5-Trimethylcyclopent-5-enylethyl 2'-methoxy-2'-trifluoromethylphenylacetate (**22**)

To a solution of (-)-2-methoxy-2-trifluoromethylphenylacetic acid (46 mg, 0.195 mmol) in benzene (3 ml) were added sequentially a small drop of DMF and oxalyl chloride (0.051 ml, 0.584 mmol) and the solution was stirred at room temperature for 45 min. The solvent was distilled under vacuum, benzene (ca. 5 ml) was added to the residue and distilled at reduced pressure. The residual acid chloride was then kept in an argon atmosphere. A solution of alcohol **20** (20 mg, 0.13 mmol) in pyridine (0.5 ml) containing a crystal of DMAP was added to the neat acid chloride prepared above (exothermic reaction). Twenty minutes later the suspension was diluted with ether and treated with aqueous hydrochloric acid. The organic layer was washed once more with acid, then with aqueous sodium bicarbonate, dried (Na_2SO_4), filtered and concentrated under vacuum to a colorless

oil. Chromatographic filtration of this oil over silica gel delivered ester **22** (48 mg, 100%) as a colorless oil: ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.57 (m, 2H), 7.43 (m, 3H), 5.24 (br.s, 1H, =CH-), 4.43 (ddd, 1H, J = 10.5, J' = 8, J" = 5 Hz, $-CH_2O-$), 4.34 (dt, 1H, J = 10.5, 8 Hz, $-CH_2O-$), 3.60 (d, 3H, J = 2 Hz, $-OCH_3$) 2.27 (m, 1H), 1.84 (m, 3H), 1.62 (m, 1H), 1.62 (t, 3H, J = 3 Hz, $CH_3C=$), 0.98 (s, 3H, $-CH_3$) and 0.80 (s, 3H, $-CH_3$). ^{19}F nmr (376 MHz, $CDCl_3$) δ 42.3788 (s, $-CF_3$).

5-Carbomethoxymethyl-6,6-dimethyl-2-cyclohexene-1-one (**24**)

Ester **19** (5 g, 27.0 mmol) was dissolved in methylene chloride (20 ml) and methanol (20 ml). The solution was chilled to -78°C and a stream of ozone was passed through until a pale blue color persisted. After flushing with oxygen for 10 min, a solution of triphenylphosphine (7.86 g, 30 mmol) in methylene chloride (20 ml) was added. The cryogenic bath was removed and the mixture allowed to come to room temperature and stirred 10 hr thereafter. The solvent was taken off *in vacuo* and the residual oil dissolved in benzene (100 ml). *p*-Toluenesulfonic acid hydrate (536 mg, 2.8 mmol) was added and the mixture was brought to reflux for 5 hr using a Dean-Stark water separator. The solvent was evaporated under vacuum and

the residue was treated with ether. The precipitated triphenylphosphine oxide was filtered and washed with ether. The residue obtained after solvent removal was distilled at reduced pressure to give enone **24** (3.3 g, 61%) as an almost colorless liquid: b.p. 100°C/2 torr. ^{1}H nmr (200 MHz, $CDCl_3$) δ 6.93 (ddd, 1H, J = 3, J' = 10.4, J" = 5 Hz, -CH=CHCO-), 5.96 (dt, 1H, J = 10.5, J' = 1.5 Hz, -CH=CHCO-), 3.70 (s, 3H, $-OCH_3$), 2.64-2.1 (m, 5H), 1.19 (s, 3H, $-CH_3$) and 1.02 (s, 3H, $-CH_3$). ^{13}C nmr (15 MHz, $CDCl_3$) δ 203.16, 173.03, 146.93, 128.12, 51.66, 44.85, 40.47, 34.87, 29.21, 22.45 and 19.11. ir (neat) 1740 (ester C=O) and 1680 cm^{-1} (enone C=O). ms M^+ 196.1097 (calcd. for $C_{11}H_{16}O_3$: 196.1099). Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.31; H, 8.22. Found: C, 67.34; H, 8.28.

(2S*,3S*,5S*)-5-Carbomethoxymethyl-6,6-dimethyl-2,3-epoxycyclohexanone (**26**)

Enone **24** (250 mg, 1.273 mmol) was dissolved in methanol (2.5 ml) and the solution was cooled to 0°C. Hydrogen peroxide (0.43 ml of a 30% solution, 3.82 mmol) was added followed by a solution of lithium hydroxide hydrate (10.7 mg, 0.255 mmol) in water (1 ml). The solution was stirred at 0°C for 30 min under an atmosphere

of argon. The solvent was evaporated under vacuum (<25°C) and the residue was partitioned between aqueous sodium chloride and methylene chloride. The organic extract was washed once with aqueous sodium chloride, dried (Na_2SO_4), filtered and concentrated to a colorless oil. Distillation of this oil at reduced pressure provided epoxide **26** (247 mg, 92%) as a colorless oil: b.p. 130°C/0.8 torr. ^1H nmr (400 MHz, $CDCl_3$) δ 3.72 (s, 3H, $-OCH_3$), 3.56 (td, 1H, J = 4, J' = 1 Hz, $-CH_2\underline{C}HO-$), 3.26 (d, 1H, J = 4 Hz, -CHCO-), 2.47 (m, 2H), 2.37 (dt, 1H, J = 16, J' = 4 Hz, $-\underline{C}H_2CHO-$), 2.12 (dd, 1H, J = 17, J' = 10 Hz, $-CH_2CO_2-$), 1.82 (ddd, 1H, J = 16, J' = 12, J" = 1 Hz, $-\underline{C}H_2CHO-$), 1.17 (s, 3H, $-CH_3$) and 0.93 (s, 3H, $-CH_3$). ^{13}C nmr (15 MHz, $CDCl_3$) δ 208.45, 172.85, 53.38, 51.67, 45.52, 34.51, 32.67, 26.65, 22.62 and 19.18. ir (neat) 1738 (ester C=O) and 1710 cm^{-1} (ketone C=O). ms M^+ 212.1042 (calcd. for $C_{11}H_{16}O_4$: 212.1048). Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.23; H, 7.60. Found: C, 62.61; H, 7.68.

(2S*,3S*,5S*)-5-Carbomethoxymethyl-6,6-dimethyl-2,3-epoxy-1-oximinocyclohexane (**27**)

Ketone **26** (400 mg, 1.89 mmol) was dissolved in methanol (6 ml). Sodium acetate (493 mg, 6.01 mmol) and hydroxylamine hydrochloride (181.6 mg, 2.632 mmol) were

added followed by water (4 ml) and the solution was stirred at room temperature for 18 hr under an argon atmosphere. Water was added and the product was extracted with methylene chloride. Drying (Na_2SO_4), filtration and solvent removal gave a yellow oil which soon crystallized. Recrystallization from benzene-methylene chloride afforded oxime **27** (360 mg, 84%) as a white solid: m.p. 112-113.5°C. ^1H nmr (400 MHz, $CDCl_3$) δ 9.20 (s, 1H, =NOH), 4.06 (d, 1H, J = 4 Hz, -CHC=), 3.70 (s, 3H, $-OCH_3$), 3.45 (dt, J = 4, J' = 2.2 Hz, =CCH-), 2.54 (dd, 1H, J = 14, J' = 3.5 Hz, $-CH_2CO-$), 2.26 (ddd, 1H, J = 14, J' = 4.5, J" = 1.5 Hz, $-\underline{CH_2}CHO-$), 2.12 (m, 1H, $-CH_2\underline{CH}CH_2-$), 2.06 (dd, 1H, J = 10, J' = 14 Hz, $-CH_2CO-$), 1.73 (ddd, 1H, J = 14, J' = 10, J" = 2.5 Hz, $-\underline{CH_2}CHO-$), 1.19 (s, 3H, $-CH_3$) and 1.00 (s, 3H, $-CH_3$). ^{13}C nmr (15 MHz, $CDCl_3$) δ 173.32, 159.88, 51.85, 51.61, 43.87, 37.67, 34.82, 33.65, 27.50, 22.82 and 20.50. ir ($CHCl_3$) 3600 (sharp, OH), 3320 (broad, OH) and 1730 cm^{-1} (ester C=O). ms M^+ 227.1156 (calcd. for $C_{11}H_{17}NO_4$: 227.1157). Anal. Calcd. for $C_{11}H_{17}NO_4$: C, 58.12; H, 7.54; N, 6.16. Found: C, 58.07; H, 7.60; N, 5.88.

cis,trans-5-Carbomethoxymethyl-3-methoxy-4,4,6-trimethyl-2-cyclohexene-1-one (36)

Ketoacid **14** (100 mg, 0.472 mmol) was dissolved in methanol (1.5 ml). Trimethyl orthoformate (1.25 ml, 11.44 mmol) was added, followed by 15 drops of conc. sulfuric acid (caution). The solution was then immersed in an oil bath preheated to 70°C. After 15 min the mixture was cooled to ambient temperature and water (10 ml) was added. The product was extracted with methylene chloride. The organic extracts were washed with water, dried (Na_2SO_4), filtered and concentrated to give a colorless oil. Chromatographic filtration through silica gel (100% $CHCl_3$) afforded vinylogous ester **36** (108 mg, 96%) as a colorless oil. This compound was found to be a mixture of two epimers in a *ca.* 2:1 ratio and displayed the following spectral characteristics: ^1H nmr (200 MHz, $CDCl_3$) δ 5.29 (s), 5.22 (s, 1H total, =CHCO-), 3.68 (s), 3.665 (s), 3.66 (s), 3.64 (s, 3H total, $-OCH_3$), 2.6-2.2 (m, 4H), 1.18, 1.13, 1.12, 1.10, 1.09 and 1.08 (9H total). ir (neat) 1743 (ester and ketone C=O), 1663 and 1613 cm^{-1} (vinyl ether). ms M^+ 240.1361 (calcd. for $C_{13}H_{20}O_4$: 240.1361). *Anal.* Calcd. for $C_{13}H_{20}O_4$: C, 64.96; H, 8.39. Found: C, 65.02; H, 8.31.

6-Carbomethoxymethyl-4-methoxy-1,5,5-trimethyl-2-trimethylsilyloxycyclohexa-1,3-diene (40)

Vinylogous ester **36** (60 mg, 0.25 mmol) was dissolved in triethylamine (3 ml), under an argon atmosphere. Trimethylsilyl trifluoromethanesulfonate (0.165 ml, 0.75 mmol) was added *via* syringe and the mixture was stirred for 0.5 hr. Pentane was added and the supernatant decanted from the oily $Et_3\overset{+}{N}H\ \overset{-}{O}T_F$. This oil was washed once more with pentane. The solvent was removed *in vacuo*. Pentane was again added, decanted and distilled to provide diene **40** (78 mg, 100%) homogeneous by ^1H nmr. This moisture sensitive product was not purified further: ^1H nmr (400 MHz, $CDCl_3$) δ 4.62 (s, 1H, =CH-), 3.62 (s, 3H, $-OCH_3$), 3.51 (s, 3H, $-OCH_3$), 2.49 (dd, 1H, J = 16, J' = 10 Hz, $-CH_2CO-$), 2.17 (m, 2H), 1.59 (s, 3H, $CH_3C=$), 1.05 (s, 3H, $-CH_3$), 0.95 (s, 3H, $-CH_3$) and 0.15 (s, 9H, $(CH_3)_3Si-$). ir (neat) 1735 (ester C=O), 1660 and 1609 cm^{-1} (vinyl ether).

Methyl 2-(4-methyl-3-oxocyclohexyl)-2-(2,2,3-trimethyl-cyclopent-3-enyl)acetate (44)

Diisopropylamine (0.96 ml, 6.87 mmol) was dissolved

in THF (15 ml) at -70°C under an atmosphere of argon. A solution of methyllithium in ether (1.33 M, 4.25 ml, 5.66 mmol) was slowly added via syringe and the solution was stirred for 15 min. Then a solution of ester **19** (1.0 g, 5.495 mmol) in THF (11 ml) was added dropwise from a pressure-equalizing dropping funnel. After 90 min at -70°C, a solution of 6-methyl-2-cyclohexenone (786 mg, 7.143 mmol) in THF (10 ml) was also added slowly. Five minutes later the cryogenic bath was removed and the mixture was permitted to warm up to room temperature. Addition of aqueous ammonium chloride was followed by extraction of the aqueous solution with ether. The organic extracts were washed once with water, dried (Na_2SO_4), filtered and concentrated to a yellow oil, which was purified by column chromatography. Elution with 10% pentane in chloroform removed some ester **19** (145 mg, 14.5%). Further elution with 100% $CHCl_3$ removed the remaining enone. The product was then eluted with 5% ether in chloroform. In this way compound **44** (1.033 g, 78.6% based on consumed starting material) was isolated as a pale yellow oil: ^1H nmr (100 MHz, $CDCl_3$) δ 5.24 (br.s, 1H, =CH-), 3.74 (s), 3.72 (s, 3H total, $-OCH_3$), and 1.59 (br.s, 3H, $CH_3C=$). ir (neat) 1722 cm^{-1} (C=O). ms M^+ 292.2036 (calcd. for $C_{18}H_{28}O_3$: 292.2038).

Methyl 2-((1S*,2S*,4R*)-2-benzoyl-4-methyl-3-oxocyclohexyl)-2-(2,2,3-trimethylcyclopent-3-enyl)acetate (45)

Diisopropylamine (0.29 ml, 2.06 mmol) was dissolved in THF (3 ml) under an argon atmosphere at -70°C. A solution of methyllithium in ether (1.6 M, 1.11 ml, 1.78 mmol) was added via syringe. This was followed after 15 minutes by the addition of a solution of ester **19** (300 mg, 1.648 mmol) in THF (3.5 ml) from a pressure-equalizing dropping funnel. After stirring for 90 min, a solution of 6-methyl-2-cyclohexenone (200 mg, 1.813 mmol) in THF (3 ml) was injected and the mixture was stirred for 0.5 hr. Then it was warmed up to 0°C, recooled to -70°C and quenched by the addition of a solution of freshly distilled benzoyl chloride (0.23 ml, 1.98 mmol) in THF (2 ml). After stirring overnight at room temperature, aqueous ammonium chloride was added and the product was extracted with ethyl acetate. The organic extracts were washed once with water, dried (Na_2SO_4), filtered and concentrated in vacuo to give a yellow oil. Crystallization occurred on standing. Washing the solid with isopentane delivered diketone **45** (183 mg, 28%) as white crystals, homogeneous on TLC: m.p. 180-180.5°C. ^1H

nmr (400 MHz, $CDCl_3$) δ 7.82 (d, 2H, J = 8 Hz), 7.55 (t, 1H, J = 8 Hz), 7.46 (t, 2H, J = 8 Hz), 5.25 (br.s, 1H, -CH=), 4.16 (d, 1H, J = 13 Hz, -CHCOØ), 3.43 (s, 3H, $-OCH_3$), 2.75 (dddd, 1H, J = 15, J' = 15, J" = 3, J"' = 3 Hz), 2.66 (dd, 1H, J = 12, J' = 4 Hz), 2.54 (ddq, 1H, J = 13, J' = 6, J" = 7 Hz), 2.40-2.08 (m, 5H), 1.92 (ddd, 1H, J = 25, J' = 12, J" = 3 Hz), 1.57 (br.s, 3H, CH_3C=), 1.39 (ddd, 1H, J = 28, J' = 12, J" = 6 Hz), 1.03 (d, 3H, J = 7 Hz, $CH_3\underline{CH}$-), 0.90 (s, 3H, CH_3-) and 0.72 (s, 3H, CH_3-). ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 208.91, 197.70, 174.42, 148.69, 138.54, 132.78, 128.53, 127.92, 120.62, 61.80, 57.70, 48.85, 47.55, 47.05, 46.00, 42.62, 34.38, 33.58, 26.05, 24.95, 19.50, 14.26 and 12.51. FTIR ($CHCl_3$ cast) 1738 (ester C=O), 1708 (ketone C=O), 1679 (aromatic C=O), 760 and 690 cm^{-1} (aromatic). ms M^+ 396.2296 (calcd. for $C_{25}H_{32}O_4$: 396.2301).

Methyl 2-(3-ethylenedioxy-4-methylcyclohexyl)-2-(2,2,3-trimethylcyclopent-3-enyl)acetate (**46**)

To a solution of ketoester **44** (100 mg, 0.357 mmol) in benzene (8 ml) were added ethylene glycol (0.24 ml, 4.29 mmol) and a few crystals of camphorsulfonic acid. The mixture was heated at reflux for 12 hr with continuous separation of water. After cooling to ambient temperature

water was added and the product was extracted with ethyl acetate. The organic extracts were washed with aqueous sodium bicarbonate, dried (Na_2SO_4), filtered and concentrated in vacuo to an amber oil, which was purified by column chromatography. Elution with 5% ether in chloroform afforded ketal **46** (122 mg, 105%) as a colorless viscous oil: ^1H nmr (100 MHz, $CDCl_3$) δ 5.25 (br.s, 1H, =CH-), 3.97 (br.s, 4H, $-CH_2O-$), 3.69,3.68 (s, 3H total, $-OCH_3$), 1.59 (br.s, 3H, $CH_3C=$), 0.89 (s, 3H, $-CH_3$) and 0.82 (s, 3H, $-CH_3$). ir (neat) 1740 (ester C=O) and 1090 cm^{-1} (ketal). ms M^+ 336.2301 (calcd. for $C_{20}H_{32}O_4$: 336.2301).

2-(3-Ethylenedioxy-4-methylcyclohexyl)-2-(2,2,3-trimethyl-cyclopent-3-enyl)ethanol (**47**)

Solid lithium aluminum hydride (45.2 mg, 1.19 mmol) was added in one portion to a solution of ester **46** (100 mg, 0.3 mmol) in ether (7 ml). The suspension was heated at reflux for 2 hr under an atmosphere of argon. After cooling to room temperature, aqueous sodium potassium tartrate was carefully added and the solution was extracted with ethyl acetate. The extracts were dried (Na_2SO_4), filtered and concentrated in vacuo to deliver alcohol **47** (91 mg, 100%) as a colorless oil, homogeneous

on TLC: ^1H nmr (80 MHz, $CDCl_3$) δ 5.26 (br.s, 1H, =CH-), 3.95 (br.s, 4H, $-CH_2O-$), 3.76 (m, 2H, $-C\underline{H_2}OH$), 1.08 (s, 3H, $-CH_3$) and 0.85 (s, 3H, $-CH_3$). ir (CCl_4 cast) 3460 (OH) and 1092 cm^{-1} (ketal). ms M^+ 308.2358 (calcd. for $C_{19}H_{32}O_3$: 308.2351).

2-(3-Ethylenedioxy-4-methyl)-2-(2,2,3-trimethylcyclopent-3-enyl)acetaldehyde (**48**)

Pyridinium chlorochromate (91 mg, 0.424 mmol) was dissolved in methylene chloride (2 ml). Sodium acetate (ca. 10 mg) and a solution of alcohol **47** (87 mg, 0.282 mmol) in methylene chloride (2 ml) were added in succession and the mixture was stirred at room temperature for 45 min. Ether was added and the dark suspension filtered through a column of Florisil (previously washed with 4% triethylamine in ether followed by 100% ether). Elution with ether afforded aldehyde **48** (84 mg, 98%) as a colorless oil: ^1H nmr (100 MHz, $CDCl_3$) δ 9.88, 9.84, 9.79 (s, 1H total, -CHO), 5.27 (br.s, 1H, =CH-), 3.94 (br.s, 4H, $-CH_2O-$), 0.94, 0.88, 0.82 and 0.78 (s, 6H total, $-CH_3$). ir (neat) 2720, 1715 (-CHO) and 1090 cm^{-1} (ketal). ms M^+ 306.2185 (calcd. for $C_{19}H_{30}O_3$: 306.2195).

2-(3-Ethylenedioxy-4-methyl)-2-(2,2,3-trimethylcyclopent-3-enyl)-1-methoxyethene (**49**)

Potassium hydride (591 mg of a 24% dispersion in oil, 3.55 mmol) was rinsed three times with pentane under an argon atmosphere. A solution of aldehyde **48** (155 mg, 0.507 mmol) in DMF (1.5 ml) was added dropwise. The mixture was stirred at room temperature for ca. 10 min and then methyl iodide (0.32 ml, 5.07 mmol) was added in one portion and the mixture was stirred one hour thereafter. Water was added and the solution was extracted with ether. Drying (Na_2SO_4), filtration and concentration delivered a yellowish oil, which was purified by column chromatography. Elution with 1% triethylamine in chloroform afforded compound **49** (144 mg, 89%) as a pale yellow viscous oil. For larger scale experiments, cooling with ice prior to the addition of methyl iodide is necessary: ^1H nmr (100 MHz, $CDCl_3$) δ 5.92, 5.79 (br.s, 1H total, -OCH=), 5.28 (br.s, 1H, =CH-), 3.93 (br.s, 4H, $-CH_2O-$), 3.55, 3.52, 3.50 (s, 3H total, $-OCH_3$), 0.99, 0.97, 0.90 and 0.82 (s, 6H total, $-CH_3$). ir (neat) 1655 cm^{-1} (vinyl ether). ms M^+ 320.2343 (calcd. for $C_{20}H_{32}O_3$: 320.2351).

N-propyl-2-(3-ethylenedioxy-4-methyl)-2-(2,2,3-trimethyl-cyclopent-3-enyl)acetaldimine (**52**)

n-Propylamine (2 ml) was added to a solution of aldehyde **48** (100 mg, 0.327 mmol) in 98% ethanol (6 ml). The solution was then heated at reflux for 70 min. The solvent was removed in vacuo and the residue was chromatographed over silica gel (column prewashed with 1% triethylamine in ether). Elution with chloroform-ether-triethylamine (98:1:1) afforded imine **52** (83 mg, 73%) as a bright yellow oil: ^{1}H nmr (100 MHz, $CDCl_3$) δ 7.58 (m, 1H, -N=CH-), 5.26 (br.s, 1H, =CH-), 3.94 (br.s, 4H, $-CH_2O-$) and 3.38 (br.t, 2H, $-CH_2N=$). ir (neat) 1662 (imine) and 1088 cm^{-1} (ketal). ms M^+ 347.2821 (calcd. for $C_{22}H_{37}NO_2$: 347.2824).

(2R*,3S*)-2-Methyl-2-(2,2,3-trimethylcyclopent-3-enyl)ethanol (**53**)

Solid lithium aluminum hydride (562 mg, 14.79 mmol) was added in one portion to a solution of ester **28** (1.45 g, 7.40 mmol) in THF (50 ml). The suspension was heated to reflux for 2 hr under an argon atmosphere. After cooling to room temperature, aqueous sodium potassium tartrate was carefully added and the solution was

extracted with ethyl acetate. The organic extracts were dried (Na_2SO_4), filtered and concentrated to deliver alcohol **53** (1.242 g, 100%) as a colorless oil, homogeneous on TLC: ^1H nmr (100 MHz, $CDCl_3$) δ 5.26 (br.s, =CH-), 3.74 (dd, 1H, J = 11, J' = 4 Hz, $-CH_2O-$), 3.46 (dd, 1H, J = 11, J' = 7 Hz, $-CH_2O-$), 1.60 (br.s, 3H, $CH_3C=$), 1.05 (s, 3H, $-CH_3$), 0.97 (d, 3H, J = 6.5 Hz, $\underline{CH_3}CH-$) and 0.88 (s, 3H, $-CH_3$). ir (neat) 3320 cm^{-1} (OH).

(2R*,3S*)-2,4,4,5-Tetramethylcyclopent-5-enylacetaldehyde (54)

To a solution of alcohol **53** (1.242 g, 7.39 mmol) in methylene chloride (50 ml) were added ca. 1 g of sodium acetate and pyridinium chlorochromate (2.396 g, 11.093 mmol) and the mixture was stirred at ambient temperature for 1 hr. Dilution with ether was followed by filtration through a column of Florisil. Elution with ether afforded aldehyde **54** (1.074 g, 88%) as a colorless oil: ^1H nmr (80 MHz, $CDCl_3$) δ 9.60 (d, 1H, J = 4 Hz, -CHO), 5.26 (br.s, 1H, =CH-), 1.60 (br.s, 3H, $CH_3C=$), 1.08 (d, 3H, J = 6.3 Hz, $\underline{CH_3}CH-$), 0.98 (s, 3H, $-CH_3$) and 0.85 (s, 3H, $-CH_3$). ir (neat) 2699 and 1720 cm^{-1} (CHO).

N-Ethyl-(2R*,3S*)-2,4,4,5-tetramethylcyclopent-5-enyl-acetaldimine (55)

Aldehyde **54** (200 mg, 1.205 mmol) was dissolved in ethyl amine (5 ml). A small drop of glacial acetic acid was added and the solution was stirred at room temperature for 1 hr. The solution was then diluted with carbon tetrachloride and the solvents were evaporated under vacuum. The residual yellowish oil of imine **55** (232 mg, 100%) was homogeneous on TLC. Due to its instability this substance was not purified further: ^{1}H nmr (100 MHz, $CDCl_3$) δ 7.51 (d, 1H, J = 7 Hz, -N=CH-), 5.25 (br.s, 1H, =CH-), 3.41 (q, 2H, J = 7 Hz, $-CH_2N=$), 1.59 (br.s, 3H, $CH_3C=$), 1.21 (t, 3H, J = 7 Hz, $CH_3CH_2N=$), 1.03 (d, 3H, J = 7 Hz, CH_3CH-), 0.94 (s, 3H, $-CH_3$) and 0.89 (s, 3H, $-CH_3$). ir (neat) 1670 cm^{-1} (imine).

1-(Cyclohex-2-enyloxy)-2-methyl-2-(2,2,3-trimethylcyclopent-3-enyl)ethene (56) and 2-(cyclohex-2-enyl)-2-methyl-2-(2,2,3-trimethylcyclopent-3-enyl)acetaldehyde (57)

Potassium hydride (9.36 g of a 24% dispersion in oil, 56.39 mmol) was rinsed four times with pentane under an argon atmosphere. DMF (8 ml) was added and the suspension was cooled to 0°C. A solution of aldehyde **54** (3.12 g,

18.80 mmol) in DMF (15 ml) was added slowly. When the addition was complete, a solution of 3-bromocyclohexene (8.965 g, 56.39 mmol) in DMF (5 ml) was added dropwise. After 45 min pH 7 phosphate buffer was carefully added and the solution was extracted with chloroform. The organic extracts were washed two times with water, dried (Na_2SO_4), filtered and concentrated to a yellow oil, which was purified by column chromatography. Elution with 30% pentane in chloroform afforded aldehyde **57** (1.709 g): ^1H nmr (100 MHz, $CDCl_3$) δ 9.98, 9.86 (s, 1H total, -CHO), 5.78 (br.s, 2H, -CH=CH-) and 5.28 (br.s, 1H, =CH-). ir (neat) 2710 and 1717 cm^{-1} (CHO). ms M^+ 246.1980 (calcd. for $C_{17}H_{26}O$: 246.1984) and compound **56** (1.725 g, 80% combined): ^1H nmr (80 MHz, $CDCl_3$) δ 6.00 (br.s, 1H, =CHO-), 5.85 (br.s, 2H, -CH=CH-), 5.27 (br.s, 1H, =CH-), 4.15 (br, 1H, -CHO-), 1.00 (s, 3H, $-CH_3$) and 0.78 (s, 3H, $-CH_3$). ir (neat) 3030 (=CH) and 1655 cm^{-1} (vinyl ether). ms M^+ 246.1983 (calcd. for $C_{17}H_{26}O$: 246.1984).

Preparation of **57** by Claisen rearrangement of **56**

A solution of enol ether **56** (100 mg, 0.407 mmol) in p-cymene (5 ml) was heated at reflux for 15 hr under an argon atmosphere. The solvent was removed *in vacuo* and the residue was chromatographed over silica gel (10%

pentane in chloroform) to deliver compound **57** (80 mg, 80%), identical with an authentic sample.

1-Cyano-2-(cyclohex-2-enyl)-2-(2,2,3-trimethylcyclopent-3-enyl)-1-trimethylsilyloxyethane (**58**)

Cyanotrimethylsilane (0.14 ml, 1.057 mmol) and a crystal of magnesium iodide were added to a solution of aldehyde **57** (100 mg, 0.407 mmol) in methylene chloride (1.5 ml) and the solution was heated at reflux for 1.5 hr under an argon atmosphere. After cooling to room temperature, pentane was added, the yellow solution filtered and the solvent removed *in vacuo* to give compound **58** (128 mg, 91.4%) as a yellow oil, homogeneous on TLC: ^{1}H nmr (60 MHz, $CDCl_3$) δ 5.90 (br.s, 1H), 5.79 (br.s, 2H), 5.33 (br.s, 1H, =CH-), 4.62 (d, 1H, J = 4.5 Hz, -CHO-) and 0.25 (s, 9H, $(CH_3)_3Si$-). ir (neat) 1252 and 855 cm^{-1} ($(CH_3)_3Si$).

(2-Cyclohexene)2-(2,2,3-trimethylcyclopent-3-enyl)-propionate (**61**)

To a solution of phenyl dichlorophosphate (0.25 ml, 1.65 mmol) in DME (3 ml) was added dropwise under an argon atmosphere a solution of acid **62** (150 mg, 0.824 mmol) in

DME (3 ml) containing pyridine (0.5 ml). The addition took ca. 30 min and the suspension was stirred for an additional 30 min. Then, a solution of 2-cyclohexene-1-ol (484 mg, 4.94 mmol) in DME (3 ml) was added in one portion and stirring was continued for 24 hr at room temperature. Aqueous hydrochloric acid was added and the solution was extracted with ether. The organic extracts were dried (Na_2SO_4), filtered and concentrated. The residual oil was purified by column chromatography. Elution with 10% pentane in chloroform delivered ester **61** (181 mg, 84%) as a colorless oil. This material was contaminated with ca. 5-10% of the corresponding anhydride of **62**, which was chromatographically inseparable: ^1H nmr (80 MHz, $CDCl_3$) δ 6.00 (br.d, 1H, J = 10 Hz, -CH=CH-), 5.75 (br.d, 1H, J = 10 Hz, -CH=CH-), 5.28 (br.s, 2H, -CHO- and =CH-), 1.60 (br.s, 3H, CH_3C=), 1.15 (d, 3H, J = 6.5 Hz, CH_3CH-), 0.98 (s, 3H, $-CH_3$) and 0.88 (s, 3H, $-CH_3$). ir (neat) 3030 (=CH), 1720 (ester C=O), 1371 and 1360 cm^{-1} (CH_3). ms M^+ 262.1931 (calcd. for $C_{17}H_{26}O_2$: 262.1933).

(2R*,3S*)-2,4,4,5-Tetramethylcyclopent-5-enylacetic acid (62)

Ester **28** (3 g, 15.3 mmol) was dissolved in methanol (15 ml). A solution of lithium hydroxide hydrate (1.93 g, 45.92 mmol) in water (25 ml) was added in one portion and the solution was heated at reflux for 4 hr. After cooling to room temperature, the solution was extracted once with methylene chloride and the extract was discarded. The aqueous solution was then acidified with aqueous hydrochloric acid and extracted with methylene chloride. Drying (Na_2SO_4), filtration and solvent removal afforded acid **62** (2.72 g, 98%) as an almost colorless viscous oil, homogeneous on TLC: ^1H nmr (400 MHz, $CDCl_3$) δ 11.97 (s, 1H, $-CO_2H$), 5.25 (br.s, 1H, =CH-), 2.55 (dq, 1H, J= 10, J' = 7 Hz, $CH_3\underline{CH}$-), 2.31 (m, 1H), 2.16 (dt, 1H, J = 7, J' = 10 Hz), 1.92 (m, 1H), 1.60 (q, 3H, J = 2 Hz, CH_3C=), 1.22 (d, 3H, J = 7 Hz, $\underline{CH_3}CH$-), 1.00 (s, 3H, $-CH_3$) and 0.92 (s, 3H, $-CH_3$). ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 184.38, 148.94, 120.79, 52.69, 46.95, 40.69, 33.90, 25.85, 19.47, 17.12 and 12.52. ir (neat) 3500-2000 (CO_2H) and 1700 cm^{-1} (acid C=O). Approximately 15% of the corresponding epimer of **62** was observed in the ^1H nmr spectrum.

Preparation of 2-cyclohexene-1-ol

To a solution of 2-cyclohexene-1-one (5 g, 52.1 mmol) in methanol (70 ml) was added cerium trichloride heptahydrate (9.7 g, 26.05 mmol) and the mixture was stirred until a homogeneous solution was observed. Then solid sodium borohydide (3 g, 78.15 mmol) was added in portions. After the addition was complete, the mixture was stirred for an additional 0.5 hr. Then pH 6 phosphate buffer was added and the suspension was extracted with chloroform. Drying (Na_2SO_4), filtration and solvent removal delivered an orange oil. Distillation at atmospheric pressure afforded 2-cyclohexene-1-ol (5.4 g, 106%) as a colorless oil: b.p. 166°C (lit 164-165°C). ^1H nmr (80 MHz, $CDCl_3$) δ 5.8 (br.s, 2H, =CH-), 4.20 (br.s, 1H, -CHO-) and 2.6 (s, 1H, -OH). ir (neat) 3330 (OH) and 3028 cm^{-1} (=CH).

1-Methoxy-2-methyl-3-trimethylsilyloxy-1,3-butadiene (**78**)

Diisopropylamine (11.43 ml, 81.65 mmol), was dissolved in THF (65 ml) under an argon atmosphere at -78°C. A solution of methyllithium in ether (1.6 M, 37.5 ml, 63.75 mmol) was injected slowly through a rubber septum. Half an hour later a solution of enone **76** (5 g,

43.75 mmol) in THF (30 ml) was added dropwise from a pressure-equalizing dropping funnel over 15 min and the bright yellow solution was stirred 1 hr at -78°C. Chlorotrimethylsilane (8.32 ml, 65.93 mmol) was then added neat, dropwise, *via* syringe. The cryogenic bath was removed and the suspension was permitted to reach ambient temperature. Twenty minutes later the solvent was evaporated under vacuum and the residue was taken up in petroleum ether and filtered exhaustively. Solvent removal gave a yellow liquid. Bulb-to-bulb distillation at reduced pressure furnished diene **78** (5.4 g, 66%) as a colorless liquid: b.p. 65°C (oven temp.)/0.06 torr. ^{1}H nmr (60 MHz, $CDCl_3$) δ 6.48 (br.s, 1H, -OCH=), 4.17 (d, 1H, J = 1 Hz, H_2C=), 4.08 (d, 1H, J = 1 Hz, H_2C=), 3.61 (s, 3H, $-OCH_3$), 1.58 (d, 3H, J = 1 Hz, CH_3C=) and 0.05 (s, 9H, $(CH_3)_3Si$-). ^{13}C nmr (50.3 MHz, $CDCl_3$) δ 156.12, 147.08, 111.34, 88.94, 59.89, 9.94 and -0.01. ir (neat) 3120 (vinyl ether), 3100, 3056 ($C=CH_2$), 1654, 1590 (vinyl ether) and 855 cm^{-1} ($Si-CH_3$). ms M^+ 186.1067 (calcd. for $C_9H_{18}O_2Si$: 186.1076). Anal. Calcd. for $C_9H_{18}O_2Si$: C, 58.03; H, 9.75. Found: C, 57.73; H, 9.85.

2,4-Dimethyl-4-formyl-2-cyclohexene-1-one (79)

Diene 78 (3.8 g, 20.45 mmol) was dissolved in benzene (18 ml). Freshly distilled methacrolein (8.4 ml, 0.102 mol) and a few 3 Å molecular sieves were added and the heterogeneous mixture was heated at 120°C for 20 hr in a sealed tube with an external nitrogen pressure of 46 atm. The solvent was removed in vacuo and the residue was partitioned between methylene chloride and aqueous fluoboric acid and the two-phase system was stirred vigorously for 20 min, whereupon the aqueous layer was extracted three more times with methylene chloride. The organic extracts were washed with water, dried (Na_2SO_4), filtered and concentrated to leave a brown oil. Chromatography of this oil over silica gel (100% CH_2Cl_2) provided in order of elution the methacrolein dimer (in variable amounts) and ketoaldehyde 79 (1.518 g, 49%) as a yellow mobile liquid: uv ($CHCl_3$) ε_{257} = 5,384; ε_{306} = 2,370. ^1H nmr (200 MHz, $CDCl_3$) δ 9.56 (s, 1H, -CHO), 6.50 (br.s, 1H, -CH=), 2.53 (d, 1H, J = 8 Hz), 2.51 (d, 1H, J = 8 Hz), 2.33 (m, 1H, $-CCH_2-$), 1.95 (ddd, 1H, J = 13, J' = 8, J" = 8 Hz, $-CCH_2-$), 1.86 (d, 3H, J = 3 Hz, $CH_3C=$) and 1.32 (s, 3H, $-CH_3$). ^{13}C nmr (50.3 MHz, $CDCl_3$) δ 200.54, 197.91, 144.00, 137.27, 48.60, 33.99, 29.85, 21.27 and 16.19. ir (neat) 2718, 1720 (CHO) and 1675 cm^{-1} (ketone

C=O). ms M^+ 152.0836 (calcd. for $C_9H_{12}O_2$: 152.0837).

cis,trans-2,4-Dimethyl-1-hydroxy-4-hydroxymethyl-2-cyclohexene (**83**) and (**84**)

A solution of ketoaldehyde **79** (500 mg, 3.289 mmol) in benzene (15 ml) was cooled to 5°C under an atmosphere of argon. A 25% solution of DIBAL in toluene (4.94 ml, 7.564 mmol) was added dropwise via syringe through a septum cap. After 15 min, 1N HCl was carefully added and the product was extracted with ethyl acetate. The organic extracts were dried (Na_2SO_4), filtered and concentrated to a pale yellow oil, which was purified by silica gel chromatography. Elution with 40% methylene chloride in ether gave the trans isomer **84** (131 mg) as a colorless oil: ^1H nmr (200 MHz, $CDCl_3$) δ 5.22 (br.s, 1H, -CH=), 3.98 (br.s, 1H, =CCHO-), 3.34, 3.25 (br.AB, 2H, $-CH_2O-$), 2.51 (br, 1H, -OH), 2.40 (br, 1H, -OH), 1.92 (m, 1H), 1.77 (t, 3H, J = 1 Hz, $CH_3C=$), 1.68 (m, 2H), 1.44 (dd, 1H, J = 16, J' = 10 Hz) and 0.97 (s, 3H, $-CH_3$). ^{13}C nmr (50.3 MHz, $CDCl_3$) δ 137.27, 130.83, 70.45, 68.75, 37.54, 29.11, 27.99, 24.23 and 20.33. ir (neat) 3360 cm^{-1} (OH). ms M^+ 156.1150 (calcd. for $C_9H_{16}O_2$: 156.1150). Further elution with 100% ethyl acetate furnished the cis isomer **83** (240

mg, 72.3% combined yield) also as a colorless oil: ^{1}H nmr (200 MHz, $CDCl_3$) δ 5.21 (br.s, 1H, -CH=), 3.90 (br.s, 1H, =CCHO-), 3.41 (br.d, 1H, J = 11 Hz, $-CH_2O-$), 3.31 (br.d, 1H, J = 11 Hz, $-CH_2O-$), 2.79 (br.s, 1H, -OH), 2.53 (br.s, 1H, -OH), 1.81 (d, 3H, J = 1.5 Hz, $CH_3C=$), 1.22 (m, 2H) and 0.89 (s, 3H, $-CH_3$). ^{13}C nmr (50.3 MHz, $CDCl_3$) δ 133.66, 131.40, 71.24, 67.74, 37.62, 28.56, 26.04, 23.03 and 21.16. ir (neat) 3350 cm^{-1} (OH). ms M^+ 156.1148 (calcd. for $C_9H_{16}O_2$: 156.1150).

(1R*,4S*)-2,4-Dimethyl-1-hydroxy-4-phenylselenoacetoxymethyl-2-cyclohexene (92)

Phenylselenoacetyl chloride (**91**) (103 mg, 0.452 mmol) was dissolved in methylene chloride (4 ml) under an atmosphere of argon and the solution was chilled to -20°C. A solution of cis diol **83** (69 mg, 0.442 mmol) in methylene chloride (4 ml) was added followed by collidine (460 μl). The mixture was stirred for 1.5 hr at -20°. Water and conc. hydrochloric acid were added and the product was extracted with methylene chloride. Drying (Na_2SO_4), filtration and solvent removal gave an almost colorless oil, which was purified by silica gel chromatography. Elution with 10% ether in methylene chloride afforded ester **92** (83 mg, 53%) as a colorless

oil: ^{1}H nmr (200 MHz, $CDCl_3$) δ 7.59 (m, 2H, C_6H_5), 7.31 (m, 3H, C_6H_5), 5.18 (br.s, 1H, =CH-), 3.94 (d, 1H, J = 10 Hz, $-CH_2O-$), 3.90 (br.d, 1H, =CCHO-), 3.80 (d, 1H, J = 10 Hz, $-CH_2O-$), 3.56 (s, 2H, $-SeCH_2-$), 1.9-1.5 (m, 4H), 1.76 (m, 3H, $CH_3C=$), 1.26 (dddd, 1H, J = 12, J' = 6.5, J" = 4, J'" = 1 Hz), 0.90 (s, 3H, $-CH_3$). ir (neat) 3400 (OH), 1723 (C=O), 1578, 749 and 691 cm^{-1} (aromatic. ms M^+ 354.0734 (calcd. for $C_{17}H_{22}O_3Se$: 354.0734).

Preparation of 2-chloro-3-iodopropene

Potassium iodide (543 g, 3.27 mol) was suspended in acetone (550 ml). To this suspension was added 2,3-dichloropropene (150 g, 1.35 mol) and the mixture was heated at reflux for 3 hr. The reaction mixture was then filtered and the precipitate washed exhaustively with acetone. The solvent was distilled at atmospheric pressure using a 10 cm Vigreaux column and the residual liquid was then distilled under the water aspirator. In this way, 2-chloro-3-iodopropene (114 g, 42%) was obtained as a purple liquid: b.p. 45-60°C (ca. 20-30 torr).

1-Chloro-2,4-dimethyl-4-phenylselenoacetoxymethyl-2-cyclohexene (**93**)

To a solution of alcohol **92** (20.5 mg, 0.058 mmol) in DMF (0.3 ml) was added oxalyl chloride (0.02 ml, 0.23 mmol) via syringe at room temperature. The addition must be carried out slowly. After stirring for 1 hr water was added and the solution was extracted with ether. The organic extracts were washed with water, dried (Na_2SO_4), filtered and concentrated to a colorless oil. Purification of this oil by column chromatography (25% petroleum ether in methylene chloride) furnished chloride **93** (17 mg, 79%) as a colorless oil: ^1H nmr (200 MHz, $CDCl_3$) δ 7.62 (m, 2H), 7.33 (m, 3H), 5.27, 5.23 (br.s, 1H total, =CH-), 4.35 (t, 1H, J = 3 Hz, -CHCl), 3.89 (AB, 2H, J = 12 Hz, $-CH_2O-$), 3.83 (AB, 2H, J = 12 Hz, $-CH_2O-$), 3.58, 3.56 (s, 2H total, $-CH_2Se-$), 1.79 (t, 3H, J = 2 Hz, $CH_3C=$), 0.98 (s, 3H, $-CH_3$) and 0.92 (s, 3H, $-CH_3$). ir (neat) 3070, 3055 (aromatic), 1723 (ester C=O), 1577, 740 and 692 cm^{-1} (aromatic). ms M^+ 372.0387 (calcd. for $C_{17}H_{21}ClO_2Se$: 372.0395).

2-Methyl-2-(3-oxopentyl)cyclopentane-1,3-dione (**97**)

To a suspension of 2-methylcyclopentane-1,3-dione

(**96**) (4 g, 34.48 mmol) in DME (80 ml) under an argon atmosphere were added in succession freshly distilled ethyl vinyl ketone (5.3 ml, 51.72 mmol) and powdered 1,4-diazabicyclo[2.2.2]octane (DABCO) (1.96 g, 17.24 mmol). The solid dissolved after a few minutes. The solution was stirred at room temperature for 19 hr. Aqueous hydrochloric acid was added and the solution was extracted with chloroform. Drying (Na_2SO_4), filtration and solvent removal afforded a yellow oil. Chromatographic filtration over silica gel (100% $CHCl_3$) delivered triketone **97** (6.8 g, 100%) as a colorless liquid: ^1H nmr (60 MHz, $CDCl_3$) δ 2.85 (s, 4H, $-CH_2COC-$), 2.50 (q, 2H, J = 7 Hz, $-CH_2COEt$), 2.30 (t, 2H, J = 7 Hz, $-CCH_2CH_2-$), 1.89 (t, 2H, J = 7 Hz, CH_3CH_2-), 1.13 (s, 3H, $-CH_3$) and 1.03 (t, 3H, J = 7 Hz, CH_3CH_2-). ir (neat) 1770 (ring C=O) and 1715 cm^{-1} (chain C=O).

4,4-Dimethylbicyclo[4.3.0]non-4-en-3,8-dione (**95**)

To a solution of triketone **97** (267 mg, 1.362 mmol) in toluene (7 ml) was added p-toluenesulfonic acid hydrate (ca. 15 mg). The mixture was refluxed for 20 hr with continuous separation of water. After cooling to room temperature, ether was added and the solution was washed once with aqueous potassium bicarbonate, dried (Na_2SO_4)

and concentrated *in vacuo* to give a yellow liquid. Chromatographic filtration over silica gel (100% $CHCl_3$) furnished enone **95** (238 mg, 98%) as a pale yellow liquid: ^1H nmr (60 MHz, $CDCl_3$) δ 3.1-2.4 (m, 7H), 2.02 (m, 1H), 1.83 (br.s, 3H, $CH_3C=$) and 1.36 (s, 3H, $-CH_3$). ir (neat) 1738 (ketone), 1650 (enone C=O), 1412, 1402 ($CH_2C=O$) and 1374 cm^{-1} (CH_3).

4,5-Dimethyl-8-ethylenedioxybicyclo[4.3.0]non-4-en-3-one (98)

To a solution of enone **95** (227 mg, 1.275 mmol) in benzene (10 ml) was added ethylene glycol (0.36 ml, 6.38 mmol) and a few crystals of *p*-toluenesulfonic acid hydrate and the mixture was heated at reflux with continuous separation of water for 6 hr. After cooling to ambient temperature, aqueous potassium bicarbonate was added and the product was extracted with ether. The extracts were dried (Na_2SO_4), filtered and concentrated to furnish a yellow oil. Bulb-to-bulb distillation at reduced pressure delivered ketal **98** (258 mg, 91%) as a colorless oil: b.p. 143°C (oven temp.)/0.6 torr. ^1H nmr (60 MHz, $CDCl_3$) δ 3.99 (s, 4H, $-CH_2O-$), 2.8-1.4 (m, 8H), 1.68 (br.s, 3H, $CH_3C=$) and 1.38 (s, 3H, $-CH_3$). ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 198.13, 166.72, 128.61, 117.77, 65.61, 64.74, 47.41,

32.95, 31.66, 26.59, 25.70, 20.21 and 10.46. ir (neat) 1650 (enone C=O) and 1180-1000 cm^{-1} (ketal). ms M^+ 222.1258 (calcd. for $C_{13}H_{18}O_3$: 222.1256). Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.23; H, 8.17. Found: C, 70.39; H, 8.35.

(3R*,9R*)-4,9-Dimethyl-3-hydroxy-8-ethylenedioxy-bicyclo[4.3.0]non-4-ene (**99**)

To a solution of ketal **98** (74 mg, 0.333 mmol) in methanol (2 ml) at 0°C was added solid sodium borohydride (25.5 mg, 0.666 mmol). After 30 min aqueous sodium hydroxide was added and the mixture was extracted with ether. Drying (Na_2SO_4), filtration and concentration delivered an almost colorless oil. Chromatography of this material over silica gel, eluting with 40% petroleum ether in ether plus 2 ml of triethylamine per 100 ml of solvent, gave alcohol **99** (55 mg, 74%) as a colorless oil which crystallized on standing: m.p. 57.5-59°C. ^1H nmr (200 MHz, $CDCl_3$) δ 4.14 (br.t, 1H, J = 7 Hz, -CHO-), 3.9 (m, 4H, $-CH_2O-$), 2.32 (m, 2H), 2.10 (m, 2H), 1.92-1.50 (m, 3H), 1.66 (q, 3H, J = 1.7 Hz, $CH_3C=$), 1.34 (ddd, 1H, J = 12, J' = 3, J" = 3 Hz, $-CCH_2-$) and 1.17 (s, 3H, $-CH_3$). ^{13}C nmr (50.3 MHz, $CDCl_3$) δ 141.14, 127.80, 118.36, 71.43, 65.49, 64.71, 46.54, 31.90, 29.88, 26.53,

23.79, 22.35 and 14.34. ir (neat) 3400 (OH) and 1070-985 cm^{-1} (ketal). ms M^+ 224.1414 (calcd. for $C_{13}H_{20}O_3$: 224.1412). Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.60; H, 8.99. Found: C, 69.30; H, 8.97.

4,9-Dimethyl-8-(2-bromomethylethylenedioxy)bicyclo[4.3.0]non-4-en-3-one (130)

To a solution of bicyclic enone **95** (79 mg, 0.444 mmol) in benzene (20 ml) were added 3-bromo-1,2-propanediol (344 mg, 2.22 mmol) and p-toluenesulfonic acid hydrate (ca. 10 mg). The mixture was refluxed for 16.5 hr with continuous removal of water. After cooling to room temperature the solvent was evaporated in vacuo and the residue dissolved in acetone (10 ml). p-Toluenesulfonic acid hydrate (50 mg) dissolved in water (6 ml) was added and the mixture was stirred at room temperature for 19 hr. Aqueous sodium bicarbonate was added and the product extracted with ether. Drying ($CaCl_2$), filtration and solvent removal left a yellow oil. Purification of this material over neutral alumina (15% EtOAc in petroleum ether) afforded compound **130** (104 mg, 74%) as a pale yellow oil: ^1H nmr (200 MHz, CD_2Cl_2) δ 4.36 (m, 1H), 4.12 (m, 1H), 3.88 (m, 1H), 3.40 (m, 2H), 2.60-1.95 (m, 7H), 1.66 (br.s, 3H, $CH_3C=$), 1.59 (m, 1H), 1.265 (s), 1.260

(s), 1.24 (s) and 1.22 (s, 3H total, $-CH_3$). ir (neat) 1659, 1650 (enone C=O) and 1180-1000 cm^{-1} (ketal). ms M^+ 316.0501 (calcd. for $C_{14}H_{19}BrO_3$: 316.0497).

(3R*,9R*)-4,9-Dimethyl-3-hydroxy-8-(2-bromomethylethyl-enedioxy)bicyclo[4.3.0]non-4-ene (133)

To a solution of enone **130** (54 mg, 0.171 mmol) in methanol (2 ml) at 0°C was added sodium borohydride (13 mg, 0.342 mmol). The ice bath was removed and the mixture allowed to warm up to room temperature. Fifteen minutes later water was carefully added and the product was extracted with ether. Drying and solvent removal gave a colorless oil which was purified by flash chromatography (25% EtOAc in petroleum ether) to furnish alcohol **133** (45 mg, 83%) as a colorless viscous oil: ^1H nmr (400 MHz, $CDCl_3$) δ 4.36 (m, 1H), 4.12 (m, 1H), 3.90 (m, 0.7H), 3.81 (dd, 0.3H, J = 8, J' = 7 Hz), 3.39 (m, 0.7H), 3.32 (m, 1.3H), 2.4-1.5 (m, 7H), 1.65 (s, 3H), 1.36 (m, 1H), 1.15 (s), 1.13 (s) and 1.12 (s, 3H total). ir (neat) 3380 (OH) and 1138-1020 cm^{-1} (ketal). ms M^+ 318.0652 (calcd. for $C_{14}H_{21}BrO_3$: 318.0674). Anal. Calcd. for $C_{14}H_{21}BrO_3$: C, 52.99; H, 6.67. Found: C, 53.14; H, 6.63.

(3R*,9R*)-4,9-Dimethyl-3-pivaloyloxy-8-ethylenedioxybicyclo[4.3.0]non-4-ene (**100**)

To a solution of alcohol **99** (135 mg, 0.603 mmol) in pyridine (2 ml) were added in succession a few crystals of DMAP and pivaloyl chloride (0.096 ml, 0.783 mmol). The mixture was stirred for 3 hr at room temperature whereupon the solvent was distilled off *in vacuo* at 0-10°C and the residue was partitioned between methylene chloride and water. The aqueous solution was extracted two more times with methylene chloride. The extracts were dried (Na_2SO_4), filtered and concentrated to deliver a colorless oil. Chromatography of this material over silica gel (20% ether in petroleum ether) furnished pivalate **100** (150 mg, 81%) as a colorless oil: ^1H nmr (200 MHz, $CDCl_3$) δ 5.31 (br.t, 1H, J = 8 Hz, -CHO-), 3.93 (m, 4H, $-CH_2O-$), 2.35 (m, 2H), 2.12 (m, 2H), 1.95-1.50 (m, 3H), 1.52 (br.s, 3H, $CH_3C=$), 1.34 (ddd, 1H, J = 13, J' = 3.5, J" = 3.5 Hz), 1.22 (s, 9H, $(CH_3)_3C-$) and 1.19 (s, 3H, $-CH_3$). ^{13}C nmr (50.3 MHz, $CDCl_3$) δ 178.35, 143.03, 124.55, 118.23, 73.72, 65.50, 64.71, 46.30, 38.84, 31.82, 27.21, 26.27, 25.60, 23.92, 22.24, and 14.52. ir (neat) 1719 (ester C=O), 1390 (t-butyl) and 1070-1007 cm^{-1} (ketal). ms M^+ 308.1987 (calcd. for $C_{18}H_{28}O_4$: 308.1987). Anal. Calcd. for $C_{18}H_{28}O_4$: C, 70.08; H, 9.16. Found: C, 70.27; H, 9.13.

(3R*,9R*)-4,9-Dimethyl-3-pivaloyloxybicyclo[4.3.0]non-4-en-8-one (101)

Pivalate **100** (3.85 g, 12.5 mmol) was dissolved in acetone (190 ml) and water (40 ml). The solution was chilled to -12°C and conc. hydrochloric acid (13 ml) was added dropwise from a dropping funnel. The cooling bath was removed and the reaction mixture warmed up to 20°C in the course of 40 min and maintained there for five more minutes. Then the contents of the flask were poured slowly onto saturated aqueous sodium bicarbonate and the product was extracted with chloroform. Drying (Na_2SO_4), filtration and concentration left a pale yellow oil which soon crystallized. Recrystallization from aqueous methanol delivered ketone **101** (2.6 g, 79%) as white plates: m.p. 89-90°C. ^1H nmr (400 MHz, C_6D_6) δ 5.31 (br.t, 1H, J = 8 Hz, -CHO-), 2.1 (m, 2H), 1.95 (ddd, 1H, J = 17, J' = 7.5, J" = 3.3 Hz), 1.945 (m, 1H), 1.72 (ddd, 1H, J = 19, J' = 10.5, J" = 9.2 Hz), 1.63 (ddd, 1H, J = 14, J' = 4.5, J" = 4.5 Hz), 1.49 (m, 1H), 1.44 (br.s, 3H, CH_3C=), 1.33 (ddd, 1H, J = 14, J' = 14, J" = 3.5 Hz), 1.15 (s, 9H, $(CH_3)_3C$-) and 0.84 (s, 3H, $-CH_3$). ^{13}C nmr (50.3 MHz, $CDCl_3$) δ 219.25, 178.00, 140.00, 126.17, 72.93, 47.84, 38.56, 35.54, 27.85, 26.86, 25.05, 23.02, 22.11 and

14.26. FTIR ($CHCl_3$ cast) 1740 (ketone C=O) and 1722 cm^{-1} (ester C=O). ms M^+ 264.1726 (calcd. for $C_{16}H_{24}O_3$: 264.1725). Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.68; H, 9.16. Found: C, 72.50; H, 9.04.

4,9-Dimethylbicyclo[4.3.0]non-3,5-dien-8-one (**102**)

To a solution of ketal **100** (966 mg, 3.14 mmol) in acetone (70 ml) was added p-toluenesulfonic acid hydrate (596 mg, 3.14 mmol) and the solution was heated at 40°C for 1 hr. The solvent was evaporated in vacuo and the residue was partitioned between aqueous potassium bicarbonate and methylene chloride. The aqueous solution was extracted two more times with methylene chloride. Drying (Na_2SO_4), filtration and solvent removal delivered a pale yellow oil, which was purified by column chromatography. Elution with 100% methylene chloride afforded diene **102** (237 mg, 66%) as a pale yellow oil. ^1H nmr (200 MHz, $CDCl_3$) δ 5.78 (br.s, 1H, =CH-), 5.58 (br.s, 1H, =CH-), 3.24 (br.d, 1H, J = 24 Hz, $-CH_2CO-$), 2.88 (br.d, 1H, J = 24 Hz, $-CH_2CO-$), 2.25 (m, 2H), 1.87 (q, 3H, J = 2 Hz, $CH_3C=$), 1.84 (m, 1H), 1.43 (ddd, 1H, J = 13, J' = 12, J" = 6 Hz) and 1.12 (s, 3H, $-CH_3$). ir (neat) 3055 (=CH), 1745 (ketone C=O), 1601 (C=C), 1404 ($CH_2C=O$), 980, 832 and 813 cm^{-1} (C=C). ms M^+ 162.

(8R*,9R*)-4,9-Dimethyl-8-(3-furyl)-8-hydroxybicyclo-[4.3.0]non-3,5-diene (103)

Freshly distilled β-bromofuran (0.025 ml, 0.28 mmol) was dissolved in dry ether (1 ml) and the solution was chilled to -75°C under an argon atmosphere. A solution of t-butyllithium (1.37 M, 0.17 ml, 0.23 mmol) was injected and the pale yellow solution was stirred for 20 min. Then a solution of ketone **102** (30 mg, 0.185 mmol) in ether (1.5 ml) was added via syringe. After 15 min the cryogenic bath was removed and the solution allowed to reach ambient temperature. Aqueous hydrochloric acid was added and the mixture was extracted with ether. Drying (Na_2SO_4), filtration and concentration afforded a yellow oil which was purified by column chromatography. Elution with 100% methylene chloride gave 6 mg (20%) of the starting ketone **102**. Further elution with 20% ether in methylene chloride afforded alcohol **103** (10 mg, 29.4% at 80% conversion) as a colorless oil: ^1H nmr (200 MHz, $CDCl_3$) δ 7.33 (m, 2H, =CHO-), 6.30 (dd, 1H, J = 3, J' = 1.5 Hz, -CH=CHO-), 5.54 (br.s, 2H, =CH-), 2.90 (br.d, 1H, J = 17 Hz, $-CH_2COH$), 2.73 (dd, 1H, J = 17, J' = 4 Hz, $-CH_2COH$), 1.81 (br.s, 3H, CH_3C=) and 1.12 (s, 3H, $-CH_3$). ir (neat) 3450 (OH), 3140 (furan), 980, 876 and 840 cm^{-1} (C=C).

(3R*,9R*)-3-Benzyloxy-4,9-dimethylbicyclo[4.3.0]non-4-en-8-one (129)

Potassium hydride (11.76 g of a 24% dispersion in oil, 72.3 mmol) was rinsed five times with petroleum ether under an argon atmosphere. DME (70 ml) was added and the suspension was cooled in an ice bath. A solution of alcohol **99** (11.47 g, 36.2 mmol) in DME (40 ml) was added in portions. Neat benzyl bromide (4.56 ml, 38.37 mmol) was added in one portion. After 18 hr the solvent was removed *in vacuo*. The residue was chilled to -70°C, and *ca.* 10 ml of 1N hydrochloric acid was added, followed in succession by acetone (120 ml), water (30 ml) and conc. hydrochloric acid (20 ml; slowly). The suspension was immersed in an ice-water bath and maintained there for 3 hr. While cold, the mixture was poured slowly onto saturated sodium bicarbonate. The product was extracted with ether. Drying (Na_2SO_4), filtration and solvent removal afforded a brownish oil. Purification by column chromatography (20% ethyl acetate in petroleum ether) gave ketone **129** (7.0 g, 72%) as a pale yellow oil: ^1H nmr (400 MHz, $CDCl_3$) δ 7.31 (m, 5H), 4.64 (d, 1H, J = 12 Hz, $-CH_2O-$), 4.49 (d, 1H, J = 2 Hz, $-CH_2O-$), 3.92 (br.t, 1H, J = 8 Hz, -CHO-), 2.76-2.50 (m, 3H), 2.20 (dd, 1H, J = 18,

J' = 8 Hz), 2.18 (m, 1H), 1.81 (m, 2H), 1.74 (br.s, 3H, CH_3C=), 1.45 (ddd, 1H, J = 14, J' = 15, J" = 4 Hz) and 1.17 (s, 3H, $-CH_3$). ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 219.69, 138.94, 138.72, 128.32, 128.11, 127.56, 127.29, 77.89, 70.22, 47.99, 35.58, 28.12, 25.25, 23.06, 22.23 and 14.82. ir (neat) 3090, 3070, 3038 (aromatic), 1736 (ketone C=O), 1605, 1505, 738 and 705 cm^{-1} (aromatic). ms M^+ 270.1618 (calcd. for $C_{18}H_{22}O_2$: 270.1620). Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.95; H, 8.20. Found: C, 79.52; H, 8.19.

(3R*,9R*)-4,9-Dimethyl-7-hydroxymethylene-3-pivaloyloxy-bicyclo[4.3.0]non-4-en-8-one (**104**)

Ketoester **101** (40 mg, 0.152 mmol) was dissolved in DME (2 ml) and ethyl formate (0.4 ml) at ambient temperature under an argon atmosphere. Sodium hydride (22 mg of a 50% dispersion in oil, 0.455 mmol) was added and the suspension was heated at 55°C for 1.5 hr. After cooling to 0°C, water and aqueous sodium carbonate were added and the aqueous layer was extracted three times with ether. The extracts were discarded. The aqueous solution was then acidified to pH 2 with aqueous hydrochloric acid and extracted with methylene chloride. Drying (Na_2SO_4), filtration and solvent removal gave an orange solid.

Recrystallization from ether-hexanes afforded β-ketoaldehyde **104** (35 mg, 80%) as white plates: m.p. 127°C. ^{1}H nmr (100 MHz, $CDCl_3$) δ 9.82 (s, -CHO), 9.79 (s, -CHO), 7.22 (t, 1H total, J = 1.8 Hz, =CHO-), 5.27 (br, 1H, -CHO-), 3.19 (br.s, 2H, $=CCH_2C=$), 2.22 (m, 1H), 1.72 (m, 3H), 1.61 (br.s, 3H, CH_3C), 1.27 (s, 3H, CH_3) and 1.24 (s, 9H, $(CH_3)_3C$-). FTIR ($CHCl_3$ cast) 3160 (OH), 1724 (ester and ketone C=O) and 1390 cm^{-1} (t-butyl). ms M^+ 292.1676 (calcd. for $C_{17}H_{24}O_4$: 292.1675). Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.82; H, 8.28. Found: C, 69.90; H, 8.33.

(3R*,9R*)-4,9-Dimethyl-8-methoxymethylidene-3-pivaloyloxy-bicyclo[4.3.0]non-4-en-8-one (111)

To a solution of ketoaldehyde **104** (258 mg, 0.88 mmol) in dry methanol (5 ml) were added some 3 Å molecular sieves and p-toluenesulfonic acid hydrate (168 mg, 0.88 mmol). The mixture was stirred for 1 hr at room temperature under an argon atmosphere. Aqueous sodium bicarbonate was added and the suspension was filtered. The precipitate was rinsed with water and dried in air. In this way, vinylogous ester **111** (271 mg, 100%) was obtained as a white solid, homogeneous on TLC: m.p. 137-138.5°C. ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.26 (dd, 1H, J = 3,

J' = 2 Hz, $CH_3OC\underline{H}$=), 5.27 (br.t, 1H, J = 7 Hz, -CHO-), 3.89 (s, 3H,-OCH_3), 3.31 (dd, 1H, J = 20, J' 2 Hz, =CCH_2C=), 3.09 (ddq, 1H, J = 20, J' = 3.3, J" = 1.3 Hz, =CCH_2C=), 2.19 (m, 1H), 1.84 (ddd, 1H, J = 12.5, J' = 3.5, J" = 3.5 Hz), 1.64 (m, 1H), 1.62 (t, 3H, J = 1 Hz, CH_3C=), 1.61 (ddd, 1H, J = 13, J' = 13, J" = 3.5 Hz), 1.23 (s, 9H, $(CH_3)_3$C-) and 1.20 (s, 3H, -CH_3). ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 208.27, 178.33, 154.64, 138.57, 126.06, 113.76, 73.39, 61.72, 49.04, 38.85, 28.30, 27.16, 26.97, 25.40, 22.91 and 14.69. FTIR ($CHCl_3$ cast) 2810 (OCH_3), 1720 (ester and ketone C=O), 1629 (vinyl ether) and 1390 cm^{-1} (t-butyl). Ms M^+ 306.1842 (calcd. for $C_{18}H_{26}O_4$: 306.1831).

(3R*,8S*,9R*)-4,9-Dimethyl-8-hydroxy-7-methoxymethylene-3-pivaloyloxybicyclo[4.3.0]non-4-ene (112)

To a suspension of vinylogous ester **111** (50 mg, 0.163 mmol) in methanol (2 ml) was added cerium trichloride heptahydrate (61 mg, 0.163 mmol) and the mixture was cooled to 0°C. Solid sodium borohydride (25 mg, 0.653 mmol) was added in one portion. The ice bath was removed and the reaction was allowed to proceed for 10 min at room temperature. Aqueous sodium bicarbonate was added and the mixture was extracted with ethyl acetate. Drying

(Na_2SO_4), filtration and solvent removal afforded a colorless oil. Chromatographic filtration through neutral alumina (100% acetone) delivered alcohol **112** (44 mg, 88%) as a colorless, unstable oil: ^1H nmr (400 MHz, $(CD_3)_2CO$) δ 6.07 (dd, 1H, J = 8, J' = 3 Hz, -OCH=), 5.23 (br.t, 1H, J = 8 Hz, -CHO-), 4.01 (br.s, 1H, -CHOH), 3.58 (s, 3H, $-OCH_3$), 2.94 (br.d, 1H, J = 21 Hz, $=CCH_2C=$), 2.78 (br.d, J = 21 Hz, $=CCH_2C=$), 2.14 (s, 1H, -OH), 2.05 (m, 1H), 1.77 (ddd, 1H, J = 14, J' = 3.5, J" = 3.5 Hz), 1.64 (m, 1H), 1.52 (br.t, 3H, J = 1.5 Hz, $CH_3C=$), 1.47 (ddd, 1H, J = 14 J' = 14, J" = 3 Hz), 1.19, 1.18, 1.17 (s, 9H total, $(CH_3)_3C-$) and 0.91 (s, 3H, $-CH_3$). FTIR (CH_2Cl_2 cast) 3460 (OH), 1726 (ester C=O) and 1400 (t-butyl). ms M^+ 308.1988 (calcd. for $C_{18}H_{28}O_4$: 308.1988).

(3R*,9R*)-7-Benzylidene-4,9-dimethyl-3-pivaloyloxybicyclo-[4.3.0]non-4-en-8-one (**107**)

A solution of ketoester **101** (300 mg, 1.13 mmol) in toluene (30 ml) was treated with benzaldehyde (0.29 ml, 2.84 mmol) and sodium hydride (87 mg of a 50% dispersion in oil, 1.83 mmol). The suspension was heated at reflux under an argon atmosphere for 1.5 hr. After cooling to 10°C, 1N hydrochloric acid was added and the product was extracted with ether. Drying (Na_2SO_4), filtration and

solvent removal afforded a yellow oil. Addition of methanol caused precipitation of the product. Recrystallization from methanol afforded enone **107** (371 mg, 93%) as a white solid: m.p. 152.5-153°C. ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.62 (d, 2H, J = 8 Hz), 7.50 (m, 4H), 5.31 (br.t, 1H, J = 8 Hz, -CHO-), 3.66 (d, 1H, J = 17 Hz, $=CCH_2C=$), 3.54 (d, 1H, J = 17 Hz, $=CCH_2C=$), 2.24 (m, 1H), 1.94 (dt, 1H, J = 13, J' = 4 Hz), 1.75 (m, 2H), 1.66 (s, 3H, $CH_3C=$), 1.27 (s, 3H, $-CH_3$) and 1.25 (s, 9H, $(CH_3)_3C-$). ^{13}C nmr (50.32 MHz, $CDCl_3$) δ 208.13, 178.16, 137.77, 135.21, 133.71, 133.23, 130.48, 129.46, 128.72, 126.91, 73.17, 47.99, 38.77, 31.14, 28.24, 27.09, 25.25, 22.94 and 14.77. ir (CH_2Cl_2) 1730 (ester C=O), 1633 (ketone C=O), 746 and 705 cm^{-1} (aromatic). ms M^+ 352.2028 (calcd. for $C_{23}H_{28}O_3$: 352.2038). Anal. Calcd. for $C_{23}H_{28}O_3$: C, 78.36; H, 8.01. Found: C, 78.24; H, 7.92.

(3R*,8S*,9R*)-7-Benzylidene-4,9-dimethyl-8-hydroxy-3-pivaloxybicyclo[4.3.0]non-4-ene (**108**)

To a suspension of enone **107** (351 mg, 0.997 mmol) in methanol (35 ml) was added cerium trichloride heptahydrate (370 mg, 0.992 mmol). The mixture was cooled to 10°C and treated with solid sodium borohydride (151 mg, 3.97 mmol) added in portions. After 5 min, 1N hydrochloric acid was

added and the product was extracted with methylene chloride. Drying (Na_2SO_4), filtration and solvent removal provided a colorless oil, which was purified by column chromatography over silica gel (5% ether in methylene chloride). In this way compound **108** (353 mg, 100%) was obtained as a colorless oil, which crystallized on standing: m.p. 93°C. ^1H nmr (400 MHz, $CDCl_3$) δ 7.40 (m, 4H), 7.25 (m, 1H), 6.59 (d, 1H, J = 4 Hz, =CH-), 5.35 (br.t, 1H, J = 8 Hz, -CHO-), 4.14 (br.s, 1H, -CHOH), 3.29 (d, 1H, J = 20 Hz, $=CCH_2C=$), 3.23 (d, 1H, J = 20 Hz, $=CCH_2C=$), 2.20 (m, 2H), 1.88 (dt, 1H, J = 12, J' = 4 Hz), 1.64 (m, 2H), 1.60 (br.s, 3H, $CH_3C=$), 1.13 (s, 9H, $(CH_3)_3C-$) and 0.93 (s, 3H, $-CH_3$). ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 178.53, 143.16, 139.88, 137.35, 128.32, 126.43, 126.13, 121.58, 84.19, 73.64, 43.53, 38.84, 32.86, 30.97, 27.13, 25.55, 16.97 and 14.74. ir (neat) 3640 (OH), 3080, 3047 (aromatic), 1725 (ester C=O), 748 and 707 cm^{-1} (aromatic). ms M^+ 354.2188 (calcd. for $C_{23}H_{30}O_3$: 354.2195).

(3R*,9R*)-7-Carbomethoxy-4,9-dimethyl-3-pivaloyloxy-bicyclo[4.3.0]non-4-en-8-one (**114**) and (3R*,9R*)-3-benzyloxy-7-carbomethoxy-4,9-dimethylbicyclo[4.3.0]non-4-en-8-one (**135**)

A solution of ketoester **101** (1.0 g, 3.787 mmol) in DME (30 ml) was added slowly to sodium hydride (291 mg of a 50% dispersion in oil, 6.06 mmol, previously washed four times with petroleum ether) under an argon atmosphere. Dimethyl carbonate (1.6 ml, 18.94 mmol) was then injected and the suspension was heated at 60°C for 4 hr. The resulting mixture was cooled to 0°C and acidified with ice-cold aqueous oxalic acid until the orange color faded to yellow and then the aqueous solution was extracted with methylene chloride. Drying (Na_2SO_4), filtration and concentration delivered a brown oil which was purified by flash chromatography (10% benzene in chloroform) to furnish β-ketoester **114** (908 mg, 75%) as an orange oil, which crystallized on standing. Recrystallization from petroleum ether gave a white powder: m.p. 78-79°C. ^1H nmr (400 MHz, $CDCl_3$) δ 5.28 (br.t, 0.85H, J = 8 Hz), 5.16 (br.t, 0.15H, J = 8 Hz, -CHO-), 3.81, 3.79, 3.78 (s, 3H total, $-OCH_3$), 3.30 (t, 1H, J = 8 Hz, -COCHCO-), 3.02 (d, 2H, J = 8 Hz, $-CH_2C=$), 2.27 (m, 0.15H), 2.18 (m, 0.85H), 1.84 (m, 1H), 1.69 (m, 1H), 1.64 (s, 3H, $CH_3C=$), 1.57

(ddd, 1H, J = 14, J' = 14, J" = 3 Hz), 1.25 (s, 9H, $(CH_3)_3C$-) and 1.23 (s, 3H, $-CH_3$). FTIR (CH_2Cl_2 cast) 4000-1800 (OH), 1750 (ketone C=O) and 1732 cm^{-1} (ester C=O). ms M^+ 332.1779 (calcd. for $C_{18}H_{26}O_5$: 332.1780). Anal. Calcd. for $C_{18}H_{26}O_5$: C, 67.04; H, 8.13. Found: C, 66.96; H, 8.08. The same procedure was followed to prepare compound **135** (65%, oil). ^1H nmr (400 MHz, $CDCl_3$) δ 7.30 (m, 5H), 4.62 (d, 1H, J = 13 Hz, $-CH_2O-$), 4.47 (d, 1H, J = 13 Hz, $-CH_2O-$), 3.89 (br, 1H, -CHO-), 3.76-3.70 (s, 3H total, $-OCH_3$), 3.23 (t, 1H, J = 10 Hz, -COCHCO-), 2.97 (d, 2H, J = 8 Hz, $-CH_2C=$), 2.19 (m, 1H), 1.82 (m, 2H), 1.77, 1.75 (s, 3H total, $CH_3C=$), 1.47 (m, 1H), 1.22 and 1.21 (s, 3H total, $-CH_3$). ir (neat) 3090, 3064, 3035 (aromatic), 1755 (ketone C=O), 1725 (ester C=O), 740 and 705 cm^{-1} (aromatic). ms M^+ 328.1673 (calcd. for $C_{20}H_{24}O_4$: 328.1675).

(3R*,7S*,9R*)-7-Benzoyloxy-7-carbomethoxy-4,9-dimethyl-3-pivaloyloxybicyclo[4.3.0]non-4-en-8-one (**115**) and (3R*,7S*,9R*)-7-benzoyloxy-3-benzyloxy-7-carbomethoxy-4,9-dimethylbicyclo[4.3.0]non-4-en-8-one (**136**)

A solution of β-ketoester **114** (908 mg, 2.82 mmol) in DME (14 ml) was added to a suspension of sodium hydride (203 mg of a 50% dispersion in oil, 4.23 mmol) in DME (3

ml) at -25°C under an atmosphere of argon. One hour later, a solution of benzoyl peroxyde (751 mg, 3.1 mmol) in DME (3 ml) was injected rapidly. After 1 hr the suspension was carefully neutralized with aqueous hydrochloric acid and extracted with chloroform. The organic extracts were dried (Na_2SO_4), filtered and concentrated to give a yellow oil. Flash chromatography of this oil (1% ether in methylene chloride) delivered triester **115** (935 mg, 75%) as an almost colorless oil: ^1H nmr (200 MHz, $CDCl_3$) δ 8.02 (dd, 2H, J = 8, J' = 2 Hz), 7.61 (dddd, 1H, J = 8, J' = 8, J" = 2, J'" = 2 Hz), 7.46 (ddd, 2H, J = 8, J' = 8, J" = 2 Hz), 5.33 (br.t, 1H, J = 8 Hz, -CHO-), 3.85 (s, 3H, $-OCH_3$), 3.75 (br.d, 1H, J = 17 Hz, $-CH_2C=$), 3.14 (d, 1H, J = 17 Hz, $-CH_2C=$), 2.25 (m, 1H), 2.00-1.60 (m, 3H), 1.56 (br.s, 3H, $CH_3C=$), 1.39 (s, 3H, $-CH_3$) and 1.24 (s, 9H, $(CH_3)_3C-$). ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 208.67, 178.22, 168.02, 165.01, 136.34, 133.69, 130.05, 128.70, 128.44, 127.35, 84.31, 72.92, 53.42, 49.21, 38.81, 36.31, 29.39, 27.12, 25.09, 22.68 and 14.69. FTIR ($CHCl_3$ cast) 1770 (ketone C=O), 1730 (esters C=O), 1600, 1582 and 715 cm^{-1} (aromatic). ms M^+ 442.1987 (calcd. for $C_{25}H_{30}O_7$: 442.1991). β-Ketoester **135** yielded compound **136** under essentially identical conditions (-20°C → room temperature) (76%, pale yellow oil): ^1H nmr (200

MHz, $CDCl_3$) δ 7.99 (dd, 2H, J = 8, J' = 2 Hz), 7.5 (dddd, 1H, J = 8, J' = 8, J" = 2, J"' = 2 Hz), 7.34 (m, 7H), 4.64 (d, 1H, J = 12 Hz, $-CH_2O-$), 4.48 (d, 1H, J = 12 Hz, $-CH_2O-$), 3.99 (br.t, 1H, J = 7 Hz, -CHO-), 3.82 (s, 3H, $-OCH_3$), 3.69 (br.d, 1H, J = 18 Hz, $-CH_3C=$), 3.12 (d, 1H, J = 18 Hz, $-CH_2C=$), 2.24 (m, 1H), 1.88 (m, 3H), 1.68 (br.s, 3H, $CH_3C=$) and 1.36 (s, 3H, $-CH_3$). ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 209.18, 168.02, 164.97, 138.64, 135.01, 133.61, 130.03, 129.45, 128.81, 128.39, 128.31, 127.80, 127.54, 84.33, 77.68, 70.44, 53.39, 49.29, 36.27, 29.51, 25.15, 22.72 and 15.11. FTIR (CH_2Cl_2 cast) 3080, 3048, 3020 (aromatic), 1770 (ketone C=O), 1732 (esters C=O), 738 and 714 cm^{-1} (aromatic). ms M^+ 448.1879 (calcd. for $C_{27}H_{28}O_6$: 448.1886).

(3R*,7S*,8S*,9R*)-7-Benzoyloxy-7-carbomethoxy-4,9-dimethyl-8-hydroxy-3-pivaloyloxybicyclo[4.3.0]non-4-ene (116) and (3R*,7S*,8S*,9R*)-7-benzoyloxy-3-benzyloxy-7-carbomethoxy-4,9-dimethyl-8-hydroxybicyclo[4.3.0]non-4-ene (137)

To a solution of ketotriester 115 (70 mg, 0.158 mmol) in methanol (1.5 ml) was added sodium borohydride (12 mg, 0.317 mmol) at 0°C. After the addition, the mixture was warmed up to ambient temperature and stirred 50 min

thereafter. pH 6 phosphate buffer was added and the product was extracted with methylene chloride. Drying (Na_2SO_4), filtration and solvent removal furnished a colorless oil. Chromatographic filtration through silica gel (5% ether in methylene chloride) delivered alcohol **116** (72 mg, 100%) as a colorless viscous oil: ^1H nmr (200 MHz, $CDCl_3$) δ 8.07 (dd, 2H, J = 8, J' = 2 Hz), 7.61 (dddd, 1H, J = 8, J' = 8, J" = 2, J"' = 2 Hz), 7.47 (ddd, 2H, J = 8, J' = 8, J" = 2 Hz), 5.31 (br.t, 1H, J = 8 Hz, -CHO-), 4.15 (d, 1H, J = 5 Hz, -CHOH), 3.80 (s, 3H, $-OCH_3$), 3.65 (br.d, 1H, J = 18 Hz, $-CH_2C=$), 3.00 (d, 1H, J = 5 Hz, -CHOH), 2.77 (d, 1H, J = 18 Hz, $-CH_2C=$), 2.14 (m, 1H), 1.92 (m, 1H), 1.70 (m, 2H), 1.53 (br.s, 3H, $CH_3C=$) and 1.25 (s, 3H, $-CH_3$). ^{13}C nmr (50.3 MHz, $CDCl_3$) δ 178.43, 170.46, 166.53, 138.95, 133.46, 129.83, 129.45, 128.41, 126.47, 89.42, 88.40, 73.28, 52.71, 44.21, 38.87, 37.90, 34.69, 27.15, 25.43, 17.17 and 14.81. FTIR ($CHCl_3$ cast) 3490 (OH), 3060, 3020 (aromatic), 1747, 1722 (esters C=O), 755 and 715 cm^{-1} (aromatic). ms m/e 413.1987 (M^+ - 31; calcd. for $C_{24}H_{29}O_6$: 413.1964). Analogously, compound **137** was prepared from ketone **136** (100%, oil): ^1H nmr (400 MHz, $CDCl_3$) δ 8.03 (dd, 2H, J = 8, J' = 2 Hz), 7.45 (dd, 2H, J = 8, J' = 8 Hz), 7.35 (m, 4H), 7.28 (m, 1H), 4.64 (d, 1H, J = 12 Hz, $-CH_2O-$), 4.49 (d, 1H, J = 12

Hz, $-CH_2O-$), 4.08 (d, 1H, J = 4 Hz, -CHOH), 3.96 (br.t, 1H, J = 8 Hz, -CHO-), 3.78 (s, 3H, $-OCH_3$), 3.58 (br.d, 1H, J = 17 Hz, $-CH_2C=$), 3.02 (d, 1H, J = 4 Hz, -CHOH), 2.78 (d, 1H, J = 17 Hz, $-CH_2C=$), 2.16 (m, 1H), 1.94 (ddd, 1H, J = 13, J' = 4, J" = 4 Hz), 1.84 (m, 1H), 1.66 (br.s, 3H, $CH_3C=$), 1.47 (ddd, 1H, J = 14, J' = 13, J" = 3 Hz) and 1.22 (s, 3H, $-CH_3$). ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 170.55, 166.56, 138.85, 137.79, 133.40, 129.82, 129.55, 128.59, 128.38, 128.28, 127.74, 127.44, 89.44, 88.72, 77.95, 70.12, 52.67, 44.28, 37.95, 34.84, 25.36, 17.18 and 15.21. FTIR (CH_2Cl_2 cast) 3500 (OH), 3090, 3080, 3098, 3022 (aromatic), 1745 (CO_2Me), 1719 (benzoate C=O), 733, 716 and 696 cm^{-1} (aromatic). ms M^+ 450.2040 (calcd. for $C_{17}H_{30}O_6$: 450.2042).

(3R*,7S*,8S*,9R*)-7-Carbomethoxy-7,8-dihydroxy-4,9-dimethyl-3-pivaloyloxybicyclo[4.3.0]non-4-ene (117)

To a solution of alcohol **116** (29 mg, 0.065 mmol) in methanol (0.5 ml) was added sodium methoxide (3.5 mg, 0.065 mmol) and the mixture was heated at reflux for 2.5 hr under an argon atmosphere. Upon cooling to room temperature, pH 6 phosphate buffer was added and the product was extracted with methylene chloride. Drying, filtration and concentration delivered a colorless oil.

Flash chromatography of this oil (100% ether) afforded diol **117** (14.5 mg, 65.3%) as a colorless oil: ^{1}H nmr (200 MHz, $CDCl_3$) δ 5.30 (br.t, 1H, J = 8 Hz, -CHO-), 3.86 (s, 3H, $-OCH_3$), 3.81 (d, 1H, J = 8 Hz, -CHOH), 3.60 (s, 1H, -COH), 3.13 (br.d, 1H, J = 18 Hz, $-CH_2C=$), 2.61 (d, 1H, J = 8 Hz, -CHOH),2.53 (d, 1H, J = 18 Hz, $-CH_2C_3$ 2.13 (m, 1H), 1.74 (m, 3H), 1.57 (br.s, 3H, $CH_3C=$), 1.25 (s, 9H, $(CH_3)_3C-$) and 1.18 (s, 3H, $-CH_3$). ^{13}C nmr (50.3 MHz, $CDCl_3$) δ 178.48, 174.83, 139.58, 126.27, 92.81, 83.66, 73.44, 52.94, 44.94, 39.69 38.87, 34.53, 27.15, 25.52, 17.23 and 14.91. FTIR ($CHCl_3$ cast) 3600-3530 (OH), 1720 (C=O) and 1399 cm^{-1} (t-butyl). ms M^+ 340.1886 (calcd. for $C_{18}H_{28}O_6$: 340.1886).

(7S*,8S*)-7-Carbomethoxy-7,8-dihydroxy-4,9-dimethylbicyclo[4.3.0]nonan-3,5-diene (126)

To a solution of pivalate **117** (130 mg, 0.382 mmol) in acetone (20 ml) was added p-toluenesulfonic acid hydrate (73 mg, 0.382 mmol) and the solution was heated at reflux for 3 hr. After cooling to ambient temperature, aqueous sodium bicarbonate was added and the solution was extracted with methylene chloride. The organic extracts were dried (Na_2SO_4), filtered and concentrated to give a pale yellow oil. Chromatography of this oil over silica

gel (30% ether in chloroform) afforded diene **126** (63 mg, 69%) as a colorless oil: ^{1}H nmr (200 MHz, $CDCl_3$) δ 5.66 (br, 1H, CH_3C=C<u>H</u>-), 5.29 (s, 1H, -CH=), 4.06 (d, 1H, J = 8 Hz, -C<u>H</u>OH), 3.85 (s, 3H, $-OCH_3$), 3.54 (s, 1H, -O<u>H</u>), 2.67 (d, 1H, J = 8 Hz, -CHO<u>H</u>), 2.24 (m, 2H), 1.86 (dd, 1H, J = 16, J' = 4 Hz), 1.81 (q, 3H, J = 2 Hz, CH_3C=), 1.50 (m, 1H) and 1.11 (s, 3H, $-CH_3$). FTIR ($CHCl_3$ cast) 3440 (OH), 1733 (ester C=O), 1641 and 1614 cm^{-1} (C=C). ms M^+ 238.1208 (calcd. for $C_{13}H_{18}O_4$: 238.1205).

<u>(7S*,9R*)-7-Benzoyloxy-7-carbomethoxy-4,9-dimethylbicyclo[4.3.0]nona-3,5-diene (139) and (7S*,9R*)-7-benzoyloxy-7-carbomethoxy-4,9-dimethylbicyclo[4.3.0]nona-2,4-diene (140)</u>

<u>p</u>-Toluenesulfonic acid hydrate (786 mg, 4.136 mmol) was added to a solution of ketone **136** (1.853 g, 4.136 mmol) in acetone (130 ml) and the solution was heated at reflux for 3 hr. After cooling to room temperature, aqueous sodium bicarbonate was added and the solution was extracted with methylene chloride. Drying (Na_2SO_4), filtration and concentration yielded a yellow oil, which was purified by column chromatography over silica gel (100% CH_2Cl_2). In this fashion, the mixture of dienes **139** and **140** (1.056 g, 75%) was isolated as a yellow oil which

crystallized on standing. Recrystallization from petroleum ether-ether afforded white crystals: m.p. 117-119°C. According to ^1H nmr spectroscopy, the ratio of **139** to **140** was ca. 3.5 to 1. The mixture displayed the following spectral properties: ^1H nmr (400 MHz, $CDCl_3$) δ 8.10 (dd, J = 8, J' = 2 Hz), 8.08 (dd, 2H total, J = 8, J' = 2 Hz), 7.62 (t, 1H, J = 8 Hz), 7.48 (t, 2H, J = 8 Hz), 6.01 (s), 5.86 (dd, J = 10, J' = 3 Hz), 5.85 (br.s), 5.73 (m, 2H total, =CH-), 3.89 (s), 3.88 (s, 3H total, $-OCH_3$), 3.12 (d, J = 19 Hz), 2.58 (d, J = 19 Hz), 2.37 (m), 1.92 (m, 4H total), 1.94 (br.s, 3H, $CH_3C=$), 1.32 (s) and 1.27 (s, 3H total, $-CH_3$). FTIR ($CHCl_3$ cast) 1776 (ketone C=O), 1725 (esters C-O), 1630, 1599, 750 and 710 cm^{-1} (aromatic). ms M^+ 340.1307 (calcd. for $C_{20}H_{20}O_5$: 340.1311). Anal. Calcd. for $C_{20}H_{20}O_5$: C, 70.56; H, 5.93. Found: C, 70.36; H, 6.02.

(3R*,7S*,8S*,9R*)-7-Carboxy-7,8-dihydroxy-4,9-dimethyl-3-pivaloyloxybicyclo[4.3.0]non-4-ene (**118**)

To a solution of diol **117** (2.1 g, 6.176 mmol) in methanol (60 ml) were added lithium hydroxide hydrate (259 mg, 6.176 mmol) and water (5 ml). The solution was heated at reflux for 13 min and then cooled to room temperature, whereupon ether and aqueous sodium carbonate were added.

The aqueous layer was extracted two more times with ether. The extracts were discarded. The aqueous solution was acidified with conc. hydrochloric acid and extracted with ethyl acetate. Drying (Na_2SO_4), filtration and concentration yielded a colorless oil which crystallized on standing. Trituration with petroleum ether afforded acid **118** (1.1 g, 55%) as a white amorphous solid, homogeneous on TLC. An analytical sample was prepared by recrystallization from ether-petroleum ether: m.p. 130-131°C. ^1H nmr (200 MHz, $(CD_3)_2CO$) δ 5.26 (br.t, 1H, J = 7 Hz, -CHO-), 4.75 (br, 1H, -OH), 3.78 (s, 1H, -CHOH), 3.24 (dm, 1H, J = 16 Hz, $-CH_2C=$), 2.84 (br, 1H, -OH), 2.47 (d, 1H, J = 16 Hz, $-CH_2C=$), 2.04 (m, 1H), 1.78 (ddd, 1H, J = 12, J' = 3.5, J" = 3 Hz), 1.60 (m, 2H), 1.54 (br.s, 3H, $CH_3C=$), 1.21 (s, 9H, $(CH_3)_3C-$) and 1.18 (s, 3H, $-CH_3$). ^{13}C nmr (50.3 MHz, $(CD_3)_2CO$) δ 177.85, 175.30, 141.36, 125.31, 92.03, 83.45, 73.74, 45.14, 39.68, 34.83, 27.04, 25.93, 17.47 and 14.62. FTIR (MeOH cast) 3800-1800 (OH), 1728 (ester C=O) and 1707 cm^{-1} (acid C=O). ms m/e 224.1045 (M^+ - 88; calcd. for $C_{12}H_{16}O_4$: 224.1049).

(3R*,7S*,8S*,9R*)-7,8-Dihydroxy-4,9-dimethyl-7-hydroxymethyl-3-pivaloyloxybicyclo[4.3.0]non-4-ene (123)

To a solution of diol acid **118** (117 mg, 0.359 mmol)

in THF (5 ml) under an argon atmosphere was added borane-methyl sulfide complex (0.081 ml of neat liquid, 0.861 mmol) at 0°C. After 0.5 hr the ice bath was removed and the solution was allowed to attain ambient temperature. Nine hours later 1N hydrochloric acid was added carefully, then CH_2Cl_2 and the two-phase system was stirred vigorously for 15 min. The aqueous layer was extracted once more with methylene chloride and once with ethyl acetate. Drying (Na_2SO_4), filtration and solvent removal gave a pale yellow solid. Trituration with hot ether afforded triol **123** (23 mg, 20.5%) as a white solid, homogeneous on TLC. An analytical sample was prepared by flash chromatography (100% ether): m.p. 172-172.5°C. ^1H nmr (200 MHz, DMSO-d_6) δ 5.18 (br.t, 1H, J = 8 Hz, -CHO-), 4.92 (d, 1H, J = 6 Hz, -OH), 4.42 (s, 1H, -OH), 4.36 (t, 1H, J = 6 Hz, -OH), 3.48 (m, 3H), 2.56 (br.t, 1H, J = 16 Hz, $-CH_2C=$), 2.17 (d, 1H, J = 16 Hz, $-CH_2C=$), 1.98 (m, 1H), 1.66 (m, 1H), 1.52 (m, 2H), 1.50 (br.s, 3H, $CH_3C=$), 1.20 (s, 9H, $(CH_3)_3C-$) and 0.96 (s, 3H, $-CH_3$). FTIR ($CHCl_3$ cast) 3550-1500 (OH) and 1733 cm^{-1} (ester C=O). ms m/e 294.1827 (M^+ - 18; calcd. for $C_{17}H_{26}O_4$: 294.1831).

(1R*,4R*)-3-Carbomethoxymethyl-2,4-dimethyl-4-formyl-1-pivaloyloxycyclohex-2-ene (124)

To a solution of triol **123** (13 mg, 0.042 mmol) in methanol (0.5 ml) was added a solution of periodic acid (28.5 mg, 0.125 mmol) in water (0.3 ml). The mixture was stirred at room temperature for 10 min. Water was added and the product was extracted with methylene chloride. The organic extracts were washed with water, dried (Na_2SO_4), filtered and concentrated to provide an almost colorless oil, which was purified by column chromatography over silica gel (10% ether in methylene chloride) to deliver aldehyde **124** (8 mg, 62%) as a colorless oil: ^1H nmr (200 MHz, $CDCl_3$) δ 9.44 (s, 1H, -CHO), 5.26 (m, 1H, -CHO-), 3.68 (s, 3H, $-OCH_3$), 3.14 (d, 1H, J = 17 Hz, $-CH_2CO-$), 3.00 (d, 1H, J = 17 Hz, $-CH_2CO-$), 1.87 (m, 2H), 1.71 (m, 2H), 1.70 (br.s, 3H, $CH_3C=$) and 1.24 (s, 12H, $-CH_3$). FTIR ($CHCl_3$ cast) 1723 cm^{-1} (C=O). ms m/e 282.1818 (M^+ - 28; calcd. for $C_{16}H_{26}O_4$: 282.1831).

(3R*,7S*,9S*,10R*)-4,10-Dimethyl-8,12-dioxa-7-hydroxy-3-pivaloyloxytricyclo[7.2.1.$0^{5,10}$]dodec-4-en-11-one (**119**) and (3R*,7S*,9S*,10R*)-3-benzyloxy-4,10-dimethyl-8,12-dioxa-7-hydroxytricyclo[7.2.1,$0^{5,10}$]dodec-4-en-11-one (**147**)

Lithium hydroxide hydrate (6.6 mg, 0.157 mmol) and water (0.4 ml) were added to a solution of diol **117** (53.4 mg, 0.157 mmol) in methanol (2 ml) and the solution was heated at reflux for 15 min. After cooling to 0°C, periodic acid (143 mg, 0.628 mmol) was added in one portion. After 15 min the mixture was diluted with water and extracted with ethyl acetate. The extracts were washed with water, dried (Na_2SO_4), filtered and concentrated to a pale yellow oil. Flash chromatography (5% methanol in chloroform) furnished compound **119** (44 mg, 86%) as a colorless oil: ^1H nmr (200 MHz, $CDCl_3$) δ 5.31 (s, 1H, $-CH(O)_2$), 5.23 (br.t, 1H, J = 8 Hz, -CHO-), 2.87 (d, 1H, J = 14 Hz, $-CH_2C=$), 2.59 (br.d, 1H, J = 14 Hz, $-CH_2C=$), 2.14 (m, 1H), 1.80-1.40 (m, 3H), 1.57 (br.s, 3H, $CH_3C=$), 1.32 (s, 3H, $-CH_3$) and 1.22 (s, 9H, $(CH_3)_3C-$). ^{13}C nmr (50.3 MHz, C_6D_6) δ 177.95, 171.09, 133.97, 129.37, 105.33, 98.09, 72.79, 39.05, 38.89, 33.18, 28.45, 27.14, 24.18, 21.08 and 14.28. ir (neat) 3400 (OH), 1800 (lactone C=O) and 1715 cm^{-1} (ester C=O). ms M^+

324.1576 (calcd. for $C_{17}H_{24}O_6$: 324.1573). In an analogous fashion, diol acid **141** gave **147** (99%) as a colorless unstable oil: ^1H nmr (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.30 (s, 1H, -CHOCO-), 4.64 (d, 1H, J = 12 Hz, $-CH_2O-$), 4.50 (d, 1H, J = 12 Hz, $-CH_2O-$), 3.90 (br.t, 1H, J = 8 Hz, -CHOR), 3.90 (br, 1H, -OH), 2.86 (d, 1H, J = 16 Hz, $-CH_2C=$), 2.57 (br.d, 1H, J = 16 Hz, $-CH_2C=$), 2.19 (m, 1H), 1.77 (m, 1H), 1.70 (s, 3H, $CH_3C=$), 1.64 (ddd, 1H, J = 15, J' = 13, J" = 3 Hz), 1.48 (ddd, 1H, J = 13, J' = 3.5, J" = 3.5 Hz) and 1.30 (s, 3H, $-CH_3$). ^{13}C nmr (50.3 MHz, $CDCl_3$) δ 171.19, 138.23, 136.27, 128.94, 127.94, 127.74, 127.37, 105.66, 97.72, 77.00, 70.82, 38.95, 32.84, 28.56, 24.00, 21.25 and 14.79. FTIR ($CHCl_3$ cast) 3360 (OH), 3080, 3055, 3030 (aromatic), 1802 (lactone C=O), 732 and 696 cm^{-1} (aromatic). ms M^+ 330.1475 (calcd. for $C_{19}H_{22}O_5$: 330.1467).

(3R*,7S*,8S*,9R*)-3-Benzyloxy-7-carboxy-7,8-dihydroxy-4,9-dimethylbicyclo[4.3.0]non-4-ene (141)

Sodium methoxide (472 mg, 8.73 mmol) was added to a solution of alcohol **137** (131 mg, 0.291 mmol) in methanol (3 ml). The mixture was heated at reflux for 5 min under an argon atmosphere. After cooling to room temperature water was added and the solution was extracted two times

with ether. The extracts were discarded. The aqueous solution was then acidified to pH 1 with conc. hydrochloric acid at 0°C and then was extracted with ethyl acetate. Drying, filtration and solvent removal delivered a white solid. Trituration with petroleum ether yielded acid **141** (60 mg, 64%) as a white microcrystalline solid, homogeneous on TLC. Recrystallization from petroleum ether-acetone-ether afforded an analytical sample: m.p. 138°C. ^{1}H nmr (400 MHz, $(CD_3)_2CO$) δ 7.38 (d, 2H, J = 8 Hz), 7.34 (t, 2H, J = 8 Hz), 7.26 (t, 1H, J = 8 Hz), 4.64 (d, 1H, J = 12 Hz, $-CH_2O-$), 4.50 (d, 1H, J = 12 Hz, $-CH_2O-$), 3.98 (br.t, 1H, J = 7.5 Hz, -CHO-), 3.76 (s, 1H, -CHOH), 3.21 (br.d, 1H, J = 16 Hz, $-CH_2C=$), 2.84 (br, 1H, -OH), 2.45 (d, 1H, J = 16 Hz, $-CH_2C=$), 2.14 (m, 1H), 1.77 (m, 2H), 1.64 (br.s, 3H, $CH_3C=$), 1.42 (dd, 1H, J = 16, J' = 15 Hz) and 1.14 (s, 3H, $-CH_3$). ^{13}C nmr (100.6 MHz, $(CD_3)_2CO$) δ 175.56, 140.48, 139.98, 128.85, 128.26, 128.11, 127.86, 92.54, 83.69, 78.94, 70.44, 45.48, 39.99, 35.39, 26.18, 17.84 and 15.36. FTIR (MeOH cast) 3600-2000 (OH), 1712 (acid C=O), 738 and 700 cm^{-1} (aromatic). ms m/e 224.1052 (M^+ - 108; calcd. for $C_{12}H_{16}O_4$: 224.1049). Anal. Calcd. for $C_{19}H_{24}O_5$: C, 68.64; H, 7.28. Found: C, 68.72; H, 7.35.

(3R*,7S*,9R*)-7-Benzoyloxy-3-benzyloxy-4,9-dimethyl-7-thiomethoxycarbonylbicyclo[4.3.0]non-4-en-8-one (150)

Potassium hydride (8.14 g of a 24% dispersion in oil, 50.07 mmol) was rinsed four times with petroleum ether under an argon atmosphere. HMPA (10 ml) was added and the suspension was cooled in an ice bath. A solution of ketone **129** (6.76 g, 25.037 mmol) in S,S'-dimethyl dithiocarbonate (7.64 g, 62.62 mmol) and HMPA (8 ml) was injected slowly through a rubber septum. The mixture was permitted to attain ambient temperature and was agitated 3 hr thereafter, whereupon it was painstakingly neutralized with aqueous oxalic acid. The aqueous solution was extracted four times with ether. The ether extracts were back-washed four times with water. Drying ($CaCl_2$), filtration and concentration furnished an orange oil. Toluene (250 ml) was added and distilled *in vacuo*. This process was repeated one more time. Potassium hydride (8.14 g of a 24% disperson in oil, 50.07 mmol) was rinsed four times with petroleum ether under an argon atmosphere. DME (30 ml) was added and the suspension was cooled to 0°C. Benzoyl peroxide (9.09 g, 37.55 mmol) was added. A solution of the above orange oil in DME (45 ml) was added slowly. The flask was evacuated and refilled with argon. This process was repeated once more. The ice

bath was removed and the reaction allowed to proceed at room temperature for 16 hr. After cooling to 0°C, solid sodium iodide was added in small portions. Excess base was neutralized with aqueous oxalic acid and the solution was extracted with ether. The ether extracts were washed once with aqueous sodium thiosulfate and once with aqueous sodium bicarbonate. Drying ($CaCl_2$), filtration and concentration gave a pale orange oil, which was purified by column chromatography over silica gel. Elution with 15% ethyl acetate in petroleum ether afforded 6.2 g of a pale yellow oil, which according to ^1H nmr analysis, contained 40% of ketone **129**. The yield of **150** was 50% based on the 60% of 6.2 g of product obtained. In one occasion, when working on a very small scale, complete consumption of the starting material was observed and the product isolated displayed the following spectral data: ^1H nmr (400 MHz, CD_2Cl_2) δ 8.06 (dd, 2H, J = 8, J' = 2 Hz), 7.63 (ddd, 1H, J = 8, J' = 8, J" = 2 Hz), 7.49 (t, 2H, J = 8 Hz), 7.31 (m, 5H), 4.65 (d, 1H, J = 12 Hz, $-CH_2O-$), 4.50 (d, 1H, J = 12 Hz, $-CH_2O-$), 4.04 (br, 1H, -CHO-), 3.58 (br.d, 1H, J = 16 Hz, $-CH_2C=$), 2.96 (d, 1H, J = 16 Hz, $-CH_2C=$), 2.38 (s, 3H, $-SCH_3$), 2.28 (m, 1H), 1.88 (m, 3H), 1.65 (br.s, 3H, $CH_3C=$) and 1.31 (s, 3H, $-CH_3$). ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 209.65, 198.58,

164.10, 138.89, 136.02, 133.83, 130.37, 130.27, 128.56, 128.50, 128.44, 128.34, 128.26, 127.85, 127.76, 127.52, 90.09, 78.00, 70.38, 50.06, 37.61, 29.83, 25.20, 21.86, 15.17 and 12.02. FTIR ($CHCl_3$ cast) 3083, 3060, 3033 (aromatic), 1752 (ketone C=O), 1725 (ester C=O), 1675 (thioester C=O), 736 and 710 cm^{-1} (aromatic). ms M^+ 464.1655 (calcd. for $C_{27}H_{28}SO_5$: 464.1657).

(3R*,7R*,8S*,9R*)-3-Benzyloxy-7,8-dihydroxy-4,9-dimethyl-7-hydroxymethylbicyclo[4.3.0]non-4-ene monobenzoate (153), (154) and (155)

To a solution of thioester 150 (3.367 g containing 28% of ketone 129) in absolute ethanol (50 ml) was added solid sodium borohydride (5.51 g, 0.145 mol) at 0°C. The ice bath was removed and the suspension allowed to reach room temperature and was agitated two hours thereafter. The contents of the flask were poured onto ice and acidified with conc. hydrochloric acid until bubbling ceased. The solution was extracted with ethyl acetate. Drying (Na_2SO_4), filtration and concentration gave an almost colorless oil. Column chromatography over silica gel, eluting with 2% ether in methylene chloride afforded alcohol 152 (935 mg). Further elution with 20% ether in methylene chloride furnished a mixture of diol benzoates

153, **154** and **155** (1.183 g, 53% based on the 72% of thioester present at the onset) as a colorless oil: ^1H nmr (200 MHz, $CDCl_3$) δ 8.07 and 7.45 (m, 10H). FTIR (CH_2Cl_2 cast) 3435 (OH), 1718, 1700 (ester C=O), 730, 710 and 695 cm^{-1} (aromatic). ms M^+ 422.2087 (calcd. for $C_{26}H_{30}O_5$: 442.2093).

(3R*,7R*,8S*,9R*)-3-Benzyloxy-7,8-dihydroxy-4,9-dimethyl-7-hydroxymethylbicyclo[4.3.0]non-4-ene (**138**)

The mixture of diol benzoates **153**, **154** and **155** (40 mg, 0.095 mmol) was dissolved in methanol (2 ml) in a 25 ml erlenmeyer flask. Water (1 ml) and lithium hydroxide hydrate (30 mg, 0.71 mmol) were added. The mixture was heated on a hot plate to the boiling point for 2 min. After cooling to room temperature, water was added and the solution was extracted with ethyl acetate. Drying (Na_2SO_4), filtration and solvent removal afforded a pale yellow solid. Trituration with petroleum ether furnished triol **138** (28 mg, 93%) as a white solid, homogeneous on TLC. An analytical sample was prepared by recrystallization from ether-methylene chloride at -20°C: m.p. 129.5°C. ^1H nmr (400 MHz, $(CD_3)_2CO$) δ 7.38 (d, 2H, J = 8 Hz), 7.34 (t, 2H, J = 8 Hz), 7.27 (t, 1H, J = 8 Hz), 4.63 (d, 1H, J = 12 Hz, $-CH_2O-$), 4.49 (d, 1H, J =

12 Hz, $-CH_2O-$), 3.96 (br.t, 1H, J = 8 Hz, -CHO-), 3.75 (m, 3H), 3.59 (d, 1H, J = 10 Hz), 2.83 (s, 1H, -OH), 2.80 (dd, 1H, J = 1, J' = 1 Hz, -OH), 2.48 (br.d, 1H, J = 17 Hz, $-CH_2C=$), 2.29 (d, 1H, J = 17 Hz, $-CH_2C=$), 2.11 (m, 1H), 1.78 (ddd, 1H, J = 13, J' = 3.6, J" = 3.6 Hz), 1.71 (m, 1H), 1.62 (br.s, 3H, $CH_3C=$), 1.41 (ddd, 1H, J = 14, J' = 13, J" = 2.5 Hz) and 1.04 (s, 3H, $-CH_3$). ^{13}C nmr (100.6 MHz, CD_3OD) δ 141.09, 140.16, 129.27, 128.95, 128.53, 128.02, 92.03, 81.26, 79.77, 71.27, 68.78, 45.91, 39.23, 35.76, 26.58, 18.54 and 15.54. FTIR (MeOH cast) 3360 (OH), 3080, 3056, 3022, 733 and 697 cm^{-1} (aromatic). ms M^+ 318.1830 (calcd. for $C_{19}H_{26}O_4$: 318.1831). Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.66; H, 8.23. Found: C, 71.50; H, 8.19.

(3R*,10R*)-3-Benzyloxy-4,10-dimethyl-9-hydroxy-8-oxabicyclo[4.4.0]dec-4-en-7-one (**148**)

A solution of triol **138** (190 mg, 0.597 mmol) in acetone (10 ml) was cooled to 0°C. Periodic acid (681 mg, 2.99 mmol) was dissolved in water (5 ml) and added rapidly to the triol solution. Ten minutes later the ice bath was removed and the solution permitted to reach ambient temperature and was agitated 1 hr thereafter. Water was added and the product was extracted with ethyl acetate.

The organic extracts were washed once with water, dried (Na_2SO_4), filtered and concentrated to an oil. Column chromatography of this oil over silica gel, eluting with 25% ether in methylene chloride gave lactol **148** (107 mg, 60%) as an almost colorless oil: ^1H nmr (400 MHz, $CDCl_3$) δ 9.42 (s, -CHO), 7.25 (m, 5H), 5.16, 5.14 (s, 1H total, -C<u>H</u>OH), 4.67 (m, 1H, $-CH_2O-$), 4.49 (m, 1H, $-CH_2O-$), 4.02 (br.t, 8 Hz), 3.95 (br.t, J = 8 Hz), 3.79 (t, 1H total, J = 4 Hz, -CHO-), 3.37 (d, J = 22 Hz), 3.25 (d, J = 22 Hz), 3.09 (d, J = 18 Hz), 3.04 (d, 2H total, J = 18 Hz, $-CH_2C=$), 1.77 (s), 1.67 (s, 3H total, $CH_3C=$), 1.24 (s), 1.14 (s) and 0.96 (s, 3H total, $-CH_3$). FTIR (CH_2Cl_2 cast) 3360 (OH), 3085, 3070, 3038 (aromatic), 1729 (C=O), 746 and 704 cm^{-1} (aromatic). ms M^+ 302.1526 (calcd. for $C_{18}H_{22}O_4$: 302.1518).

<u>(3R*,9R*,10R*)-3-Benzyloxy-4,10-dimethyl-9-(3-furyl)-8-oxabicyclo[4.4.0]dec-4-en-7-one (157)</u>

β-Bromofuran (0.14 ml, 1.557 mmol) was dissolved in ether (2.5 ml) at -78°C under an atmosphere of argon. A solution of <u>t</u>-butyllithium in pentane (1.11 M, 1.1 ml, 1.225 mmol) was added rapidly and the yellow solution was stirred for forty minutes. Dry HMPA (0.052 ml, 0.298 mmol) was also injected and after ten min a solution of

lactol **148** (29.8 mg, 0.099 mmol) in ether (2 ml) was added dropwise *via* syringe. The yellowish suspension was then warmed up to room temperature and was stirred five hr thereafter. The mixture was neutralized with 1N hydrochloric acid at -78°C. Water was then added and the solution was extracted two times with ether and two times with methylene chloride. Drying (Na_2SO_4), filtration and solvent evaporation yielded an orange brown oil. Flash chromatography of this oil, eluting with 10% ether in methylene chloride, provided furyl lactone **157** (15 mg, 43%) as a yellow-orange oil, homogeneous on TLC: ^1H nmr (200 MHz, $CDCl_3$) δ 7.45 (dd, 1H, J = 2, J' = 1 Hz, =CHO-), 7.42 (dd, 1H, J = 2, J' = 2 Hz, =CHO-), 7.35 (m, 5H), 6.41 (dd, 1H, J = 2, J' = 1 Hz, -OCH=C<u>H</u>-), 4.99 (s, 1H, -CHOCO-), 4.64 (d, 1H, J = 11.5 Hz, $-CH_2O-$), 4.50 (d, 1H, J = 11.5 Hz; $-CH_2O-$), 3.91 (br.t, 1H, J = 8 Hz, -C<u>H</u>OCH_2-), 3.43 (br.d, 1H, J = 20 Hz, $-CH_2C=$), 3.36 (br.d, 1H, J = 20 Hz, $-CH_2C=$), 2.15 (m, 1H), 1.76 (m, 1H), 1.70 (d, 3H, J = 1.5 Hz, $CH_3C=$), 1.37 (m, 2H) and 1.10 (s, 3H, $-CH_3$). ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 170.28, 142.97, 141.05, 138.53, 130.51, 130.24, 128.42, 127.83, 127.70, 120.25, 109.91, 81.57, 70.70, 38.41, 33.00, 30.65, 24.17, 17.06 and 14.66. FTIR ($CHCl_3$ cast) 3135 (furan), 3080, 3054, 3022 (aromatic), 1741 (lactone C=O), 735 and 700 cm^{-1}

(aromatic). ms M^+ 352.1678 (calcd. for $C_{22}H_{24}O_4$: 352.1675).

(9R*,10R*)-4,10-Dimethyl-9-(3-furyl)-8-oxabicyclo-[4.4.0]deca-3,5-diene-7-one (**63**)

Potassium hydride (~~123 mg~~ of a 35% dispersion in oil, 1.078 mmol) was rinsed with three portions of petroleum ether under an argon atmosphere. DME (1 ml) and t-butanol (1 ml) were added at 0°C. After 1 min, a solution of lactone **157** (19 mg, 0.054 mmol) in DME (1 ml) was added rapidly. Half an hour later 1N hydrochloric acid was added until the color faded to pale yellow. The solution was extracted with ether. Drying (Na_2SO_4), filtration and concentration gave an orange oil. Flash chromatography of this material eluting with 25% ethyl acetate in petroleum ether delivered a pale yellow oil which soon crystallized. Trituration with hot petroleum ether-ether (9:1) gave diene lactone **63** (10.8 mg, 82%) as white crystals: m.p. 139°C. ^1H nmr (400 MHz, $CDCl_3$) δ 7.50 (dd, 1H, J = 2, J' = 1 Hz, =CHO-), 7.44 (dd, 1H, J = 1.7, J' = 1.7 Hz, =CHO-), 6.48 (dd, 1H, J = 1.9, J' = 0.9 Hz, -OCH=C<u>H</u>-), 6.16 (br.t, 1H, J = 4 Hz, CH_3C=C<u>H</u>-), 5.86 (s, 1H, =CHCO-), 5.14 (s, 1H, -CHO-), 2.29 (m, 2H, -C<u>H_2</u>CH=), 1.90 (q, 3H, J = 1.7 Hz, CH_3C=), 1.48 (m, 2H, -CC<u>H_2</u>-) and

1.04 (s, 3H, $-CH_3$). ^{13}C nmr (100.6 MHz, $CDCl_3$) δ 159.86, 142.90, 141.16, 136.04, 135.94, 129.44, 110.29, 110.11, 80.82, 37.35, 30.12, 22.24, 18.99 and 16.05. FTIR (CH_2Cl_2 cast) 3145, 3120 (furan) and 1701 cm^{-1} (lactone C=O). ms M^+ 244.1096 (calcd. for $C_{15}H_{16}O_3$: 244.1099).

(3R*,4S*,5R*,9R*,10R*)-3-Benzyloxy-4,10-dimethyl-4,5-epoxy-9-(3-furyl)-8-oxabicyclo[4.4.0]decan-7-one (158)

To a solution of lactone **157** (74 mg, 0.21 mmol) in chloroform (17 ml) was added solid m-chloroperbenzoic acid (364 mg of 80% acid, 1.68 mmol) in one portion. The solution was stirred at room temperature for 75 min under an argon atmosphere. The chloroform solution was then washed with aqueous sodium bisulfite, once with aqueous sodium carbonate, dried (Na_2SO_4) and concentrated to give a yellow oil. This oil was redissolved in chloroform (15 ml) and treated again with MCPBA (182 mg of 80% acid, 0.84 mmol) at room temperature for 2 hr under an argon atmosphere. Isolation of the product as described above gave a yellow oil. This material was subjected one more time to the treatment with MCPBA (182 mg of 80% acid, 0.84 mmol) for 2 hr. In this way a pale yellow oil was obtained which was purified by flash chromatography. Elution with 20% ether in methylene chloride furnished

epoxide **158** (38.5 mg, 50%) as a very pale yellow oil. Approximately 12% of starting olefin was discernible in the ^1H nmr spectrum: ^1H nmr (400 MHz, $CDCl_3$) δ 7.53 (dd, 1H, J = 2, J' = 1 Hz, =CHO-), 7.51 (dd, 1H, J = 1.8, J' = 1.8 Hz, =CHO-), 7.45 (m, 5H), 6.47 (dd, 1H, J = 1.9, J' = 0.9 Hz, -OCH=CH-), 5.42 (s, 1H, -CHOCO-), 4.72 (d, 1H, J = 12 Hz, $-CH_2O-$), 4.59 (d, 1H, J = 12 Hz, $-CH_2O-$), 3.67 (t, 1H, J = 8.7 Hz, -CHO-), 3.20 (d, 1H, J = 20 Hz, $-CH_2CO-$), 2.63 (d, 1H, J = 20 Hz, $-CH_2CO-$), 2.04 (m, 1H), 1.46 (s, 3H, $-CH_3$), 1.40 (m, 3H) and 1.18 (s, 3H, $-CH_3$). FTIR (CH_2Cl_2 cast) 3140 (furan), 3085, 3065, 3035 (aromatic), 1742 (lactone C=O), 740 and 700 cm^{-1} (aromatic). ms m/e 272.1393 (M^+ - 96; calcd. for $C_{17}H_{20}O_3$: 272.1412).

(3R*,4R*,9R*,10R*)-3-Benzyloxy-4,10-dimethyl-9-(3-furyl)-4-hydroxy-8-oxabicyclo[4.4.0]dec-5-en-7-one (**159**)

Potassium hydride (8 small drops of a 35% dispersion in oil) was rinsed four times with petroleum ether under an argon atmosphere. DME (1 ml) and t-butanol (0.5 ml) were added at 0°C. When dissolution was complete, a solution of epoxylactone **158** (40 mg, 0.109 mmol) in DME (2 ml) was added rapidly. After 15 min, 6 M hydrochloric acid was added until the color faded to pale yellow. The product was then extracted with ether. Drying (Na_2SO_4),

filtration and solvent removal delivered a yellow oil. This material was purified by flash chromatography. Elution with 4% ether in methylene chloride afforded a small amount of diene lactone **63** (ca. 1-2 mg). Further elution with 25% ether in methylene chloride furnished allylic alcohol **159** (26 mg, 65%) as an almost colorless oil: ^{1}H nmr (400 MHz, $CDCl_3$) δ 7.54 (dd, 1H, J = 2, J' = 1 Hz, =CHO-), 7.48 (dd, 1H, J = 1.8, J' = 1.8 Hz, =CHO-), 7.40 (m, 5H), 6.49 (s, 1H, =CHCO-), 6.46 (dd, 1H, J = 1.9, J' = 0.9 Hz, -OCH=CH-), 5.08 (s, 1H, -CHOCO-), 4.80 (d, 1H, J = 12 Hz, $-CH_2O-$), 4.62 (d, 1H, J = 12 Hz, $-CH_2O-$), 3.45 (dd, 1H, J = 12, J' = 4 Hz, -CHO-), 2.42 (s, 1H, -OH), 2.06 (m, 1H), 1.54 (m, 2H), 1.49 (s, 3H, $-CH_3$), 1.36 (ddd, 1H, J = 14, J' = 14, J" = 4 Hz) and 1.16 (s, 3H, $-CH_3$). FTIR (CH_2Cl_2 cast) 3440 (OH), 3140 (furan), 3085, 3065, 3035 (aromatic), 1720 (lactone C=O), 740 and 701 cm^{-1} (aromatic). ms M^+ 368.1619 (calcd. for $C_{22}H_{24}O_5$: 368.1624).

(3R*,9R*,10R*)-3-Benzyloxy-4-exomethylene-9-(3-furyl)-10-methyl-8-oxabicyclo[4.4.0]dec-5-en-7-one (**160**)

To a solution of alcohol **159** (26 mg, 0.071 mmol) in pyridine (1.7 ml) at 0°C was added thionyl chloride (0.052 ml, 0.71 mmol) under an argon atmosphere. After 1 hr the

solvent was removed under high vacuum at ca. 5°C and the semisolid residue was partitioned between aqueous sodium bicarbonate and methylene chloride. The aqueous solution was further extracted two more times with methylene chloride. The organic extracts were washed once with aqueous cupric sulfate, dried (Na_2SO_4), filtered and concentrated to give a yellow oil, which was purified by flash chromatography. Elution with 20% ethyl acetate in petroleum ether delivered the exo isomer **160** (7.5 mg, 30%) as an almost colorless oil. Further elution with 30% ethyl acetate in petroleum ether furnished the endo isomer **161** (4 mg, 16%) as a colorless oil. The exo isomer displayed the following spectral properties: ^1H nmr (200 MHz, $CDCl_3$) δ 7.50 (dd, 1H, J = 2, J' = 1 Hz, =CHO-), 7.44 (dd, 1H, J = 1.6, J' = 1.6 Hz, =CHO-), 7.38 (m, 5H), 6.45 (dd, 1H, J = 2, J' = 1 Hz, -OCH=CH-), 6.06 (s, 1H, =CHCO-), 5.60 (t, 1H, J = 2 Hz, H_2C=), 5.47 (t, 1H, J = 2 Hz, H_2C=), 5.12 (s, 1H, -CHOCO-), 4.70 (s, 2H, $-CH_2O-$), 3.95 (m, 1H, -CHO-), 2.17 (m, 1H), 1.60 (m, 3H) and 1.05 (s, 3H, $-CH_3$). FTIR (CH_2Cl_2 cast) 3130 (furan), 3085, 3060, 3033 (aromatic), 1719 (lactone C=O), 733 and 695 cm^{-1} (aromatic). ms m/e 320.1408 (M^+ - 30; calcd. for $C_{21}H_{20}O_3$: 320.1412). For the endo isomer: ^1H nmr (200 MHz, $CDCl_3$) δ 7.48 (br.s, 1H, =CHO-), 7.43 (t, 1H, J = 2

Hz, =CHO-), 7.36 (m, 5H), 6.45 (dd, 1H, J = 3, J' = 2 Hz, -OCH=CH-), 5.72 (s, 1H, =CHCO-), 5.08 (s, 1H, -CHOCO-), 5.06 (s, 2H, $-CH_2O-$), 1.87 (t, 3H, J = 1.5 Hz, $CH_3C=$) and 1.00 (s, 3H, $-CH_3$).

Methyl (2R,3R)-3-t-butoxycarbonylmethyl-5-oxo-2,4,4-trimethylhexanoate (167)

To a solution of acid **29** (255 mg, 1.045 mmol) in benzene (15 ml) were added oxalyl chloride (2.5 ml) and dimethylformamide (3 drops). The solution was immersed in a water bath maintained at ca. 45°C. After 1.5 hr, the solvents were removed in vacuo. Benzene was added to the residue and distilled under the water aspirator. The residue was dissolved in pyridine (1.5 ml) and t-butanol (0.7 ml). A few crystals of DMAP were added and the solution was stirred at room temperature for 14 hr. The solvents were distilled under vacuum and the residue was partitioned between water and ether. The aqueous layer was extracted two more times with ether. The organic extracts were washed two times with aqueous cupric sulfate, once with aqueous sodium bicarbonate, dried (Na_2SO_4), filtered and concentrated to a yellow oil. Flash chromatography (5% ether in methylene chloride)

afforded compound **167** (168 mg, 54%) as a colorless oil: $[\alpha]_D^{23}$ = -5.6° (c = 1.78, CH_2Cl_2). ^1H nmr (200 MHz, $CDCl_3$) δ 3.69 (s, 3H, $-OCH_3$), 3.02 (dt, 1H, J = 8, J' = 5 Hz, $-CH_2\underline{CH}-$), 2.48 (dq, 1H, J = 5, J' = 7 Hz, $CH_3\underline{CH}-$), 2.28 (dd, 1H, J = 16, J' = 8 Hz, $-CH_2CO-$), 2.24 (s, 3H, CH_3CO-), 2.15 (dd, 1H, J = 16, J' = 5 Hz, $-CH_2CO-$), 1.45 (s, 9H, $(CH_3)_3C-$), 1.11 (d, 3H, J = 7 Hz, $\underline{CH_3}CH-$) and 1.08 (s, 3H, $-CH_3$). ^{13}C nmr (50.3 MHz, $CDCl_3$) δ 212.84, 176.28, 171.99, 80.64, 51.77, 41.35, 39.51, 33.43, 28.32, 27.96, 25.07, 22.19, 21.21 and 13.89. FTIR (CH_2Cl_2 cast) 1732 (esters C=O) and 1705 cm^{-1} (ketone C=O). ms M^+ 300.1943 (calcd. for $C_{16}H_{28}O_5$: 300.1937).

(4R,5R)-3-t-Butoxycarbonylmethyl-4,6,6-trimethylcyclohexane-1,3-dione (166)

Lithium t-butoxide (28 mg, 0.35 mmol) was added to a solution of diester **167** (35 mg, 0.117 mmol) in DME (2 ml). The suspension was heated at reflux for 6 hr under an argon atmosphere. Then more lithium t-butoxide (15 mg, 0.187 mmol) was added and refluxing continued for another 1.5 hr. After cooling to room temperature, ice and 1N hydrochloric acid were added. The aqueous solution was extracted two times with ether and once with methylene

chloride. The organic extracts were combined, dried (Na_2SO_4), filtered and concentrated to a pale yellow oil. Purification of this oil by flash chromatography, using 3% methanol in methylene chloride afforded 11 mg (31%) of starting material. Continued elution with the same solvent system delivered dione **166** (18.7 mg, 87.4% at 69% conversion) as a colorless oil which soon crystallized. Trituration with petroleum ether gave an analytical sample: m.p. 140°C. $[\alpha]_D^{23} = -11.5°$ (c = 1.245, CH_2Cl_2). ^1H nmr (200 MHz, $CDCl_3$) δ 3.52 (d, 1H, J = 16 Hz, $-COCH_2CO-$), 3.47 (d, 1H, J = 16 Hz, $-COCH_2CO-$), 2.47 (m, 2H), 2.27 (dd, 1H, J = 6, J' = 1.5 Hz, $-CH_2CO_2-$), 2.19 (dd, 1H, J = 6, J' = 2.5 Hz, $-CH_2CO_2-$), 1.46 (s, 9H, $(CH_3)_3C-$), 1.21 (d, 3H, J = 7 Hz, $\underline{CH_3}CH-$), 1.19 (s, 3H, $-CH_3$) and 1.10 (s, 3H, $-CH_3$). FTIR ($CHCl_3$ cast) 3400-1800 (β-diketone), 1727 (ester C=O) and 1640-1500 cm^{-1} (β-diketone). ms M^+ 268.1668 (calcd. for $C_{15}H_{24}O_4$: 268.1675).

2,4-Bis-(trimethylsilyloxy)-1,5,5-trimethyl-6-trimethylsilyloxycarbonylmethylcyclohexa-1,3-diene (165)

To a solution of acid **14** (100 mg, 0.472 mmol) in triethylamine (2 ml) and s-dichloroethane (4 ml) was added trimethylsilyl trifluoromethanesulfonate (0.43 ml, 2.36

mmol) via syringe. The mixture was stirred at room temperature under an argon atmosphere for 90 min. The solvents were removed in vacuo, pentane was added to the residue and decanted. A total of three extractions were performed. The residue after solvent removal was extracted again with pentane to remove traces of the oily triethylammonium triflate. Concentration under vacuum gave diene **165** (150 mg, 77%) as a yellow oil: ^{1}H nmr (80 MHz, $CDCl_3$) δ 4.78 (br.s, 1H, =CH-), 1.63 (br.s, 3H, CH_3C=), 1.05 (s, 3H, $-CH_3$), 0.93 (s, 3H, $-CH_3$) and 0.20 (m, 9H, $(CH_3)_3Si$-). ir (neat) 1719 (ester C=O), 1650, 1610 (vinyl ether) and 850 cm^{-1} (Si-CH_3).

(4R*,5R*)-2-(2-Carbethoxyprop-2-enyl)-5-carboxymethyl-4,6,6-trimethylcyclohexane-1,3-dione (**163**)

Diketoacid **14** (400 mg, 1.89 mmol) was dissolved in s-dichloroethane (15 ml) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (1.2 ml) under an argon atmosphere. A solution of ethyl 2-bromomethylacrylate (488 mg, 2.54 mmol) in s-dichloroethane (2 ml) was added in one portion. After 2 hr at room temperature, aqueous sodium carbonate was added and the solution was extracted two times with ether. The extracts were discarded. The aqueous solution was acidified with conc. hydrochloric acid and extracted with

ethyl acetate. Drying (Na_2SO_4), filtration and concentration gave a colorless oil, which was purified by column chromatography. Elution with 5% methanol in chloroform afforded diketoacid **163** (360 mg, 59%) as a colorless viscous oil: ^1H nmr (80 MHz, $CDCl_3$) δ 6.20 (d, 1H, J = 1.5 Hz, $H_2C=$), 6.1 (br.s, 1H, $H_2C=$), 4.25 (q, 2H, J = 7 Hz, $-CH_2O-$) and 1.30 (t, 3H, J = 7 Hz, $\underline{CH_3}CH_2O-$). ir (neat) 3700-2300 (acid and β-diketone), 1695 (broad) and 1605 cm^{-1} (broad, C=O). ms M^+ 324.1570 (calcd. for $C_{17}H_{24}O_6$: 324.1573).

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